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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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W. A. L. THOMPSON
and H. P. KOPELL

JOHN RUSSELL TWISS

PRACTICAL APPLICATION OF RADIOACTIVE METALS

Transcription of a Panel Meeting

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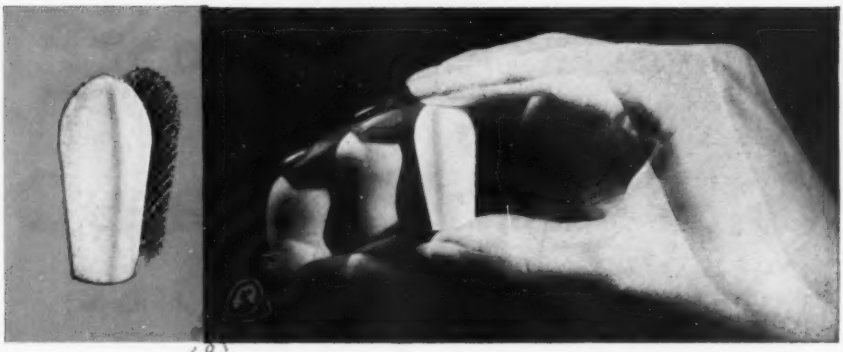

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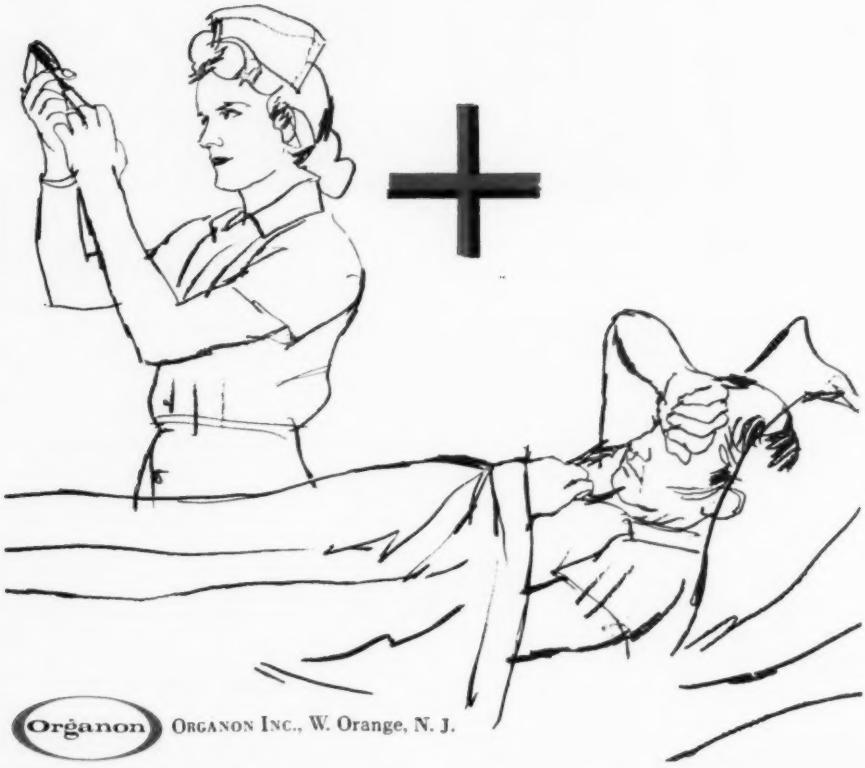

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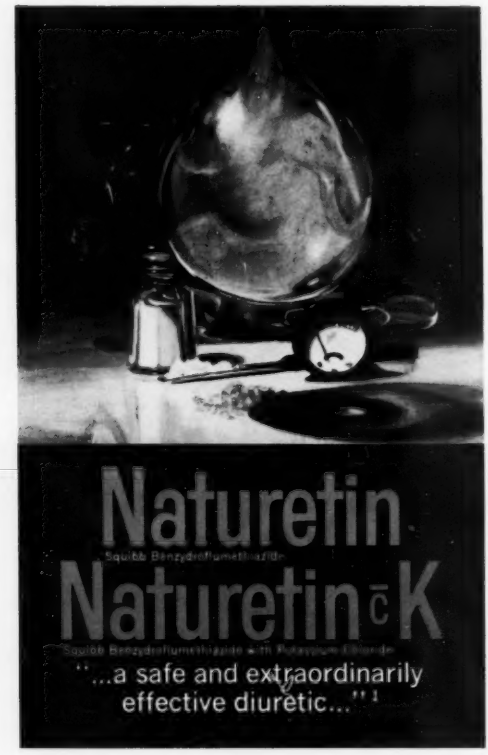

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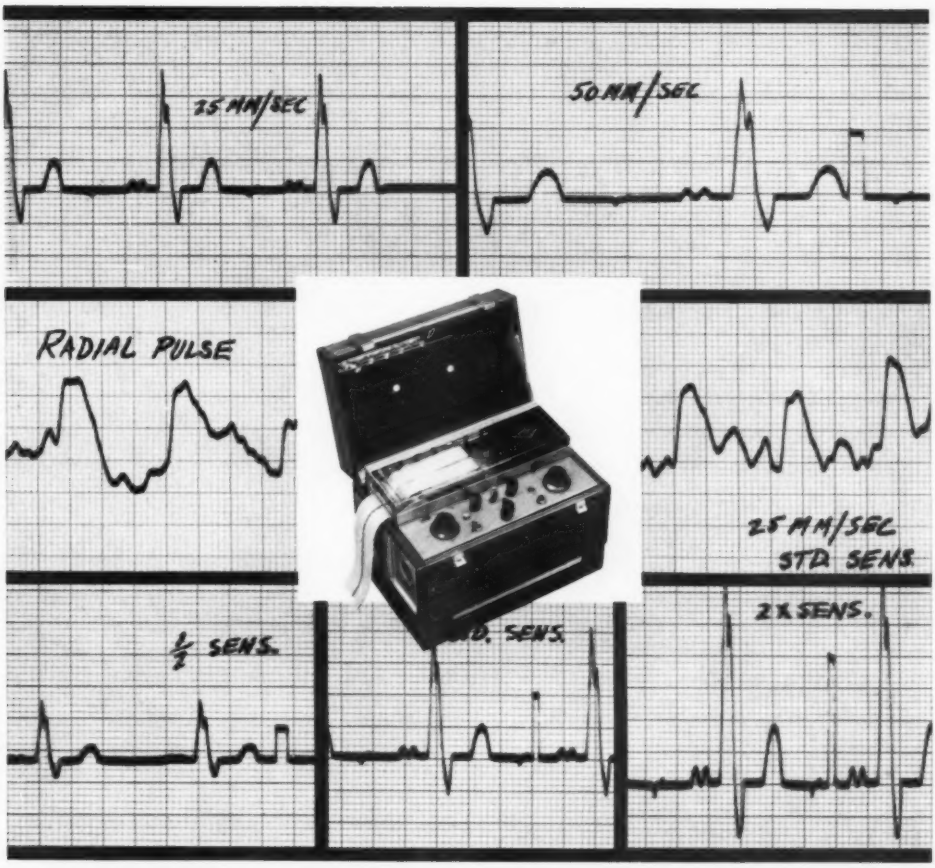

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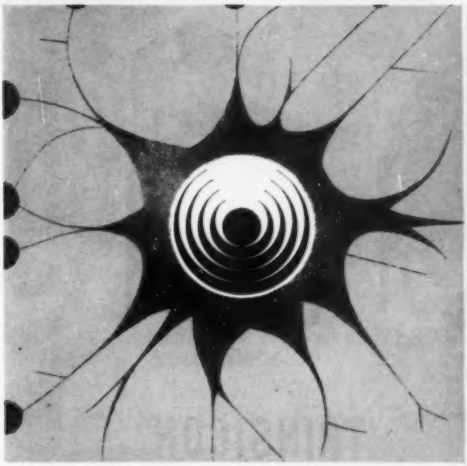

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 36, NO. 8 AUGUST 1960

THE COMPONENTS OF THE FROZEN SHOULDER*

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AND

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THE term "frozen shoulder", though in common use by orthopedic surgeons, is not often well defined. The clinical findings which delineate this condition are as follows[1]:

Pain is an outstanding complaint. It is usually the first noticed element, present at rest and becoming severe during the night.

Initially, restriction of motion seems voluntary on the basis of pain; subsequently it is noted that there is restriction of both active and passive motion.

* Presented in part by Dr. Kopell at The New York Academy of Medicine before a combined meeting of the Section on Orthopedic Surgery and the Philadelphia Orthopaedic Club, March 9, 1959. From the Neuro-Muscular Study Group, New York University-Bellevue Medical Center. Supported by the Charles A. Dana Foundation.

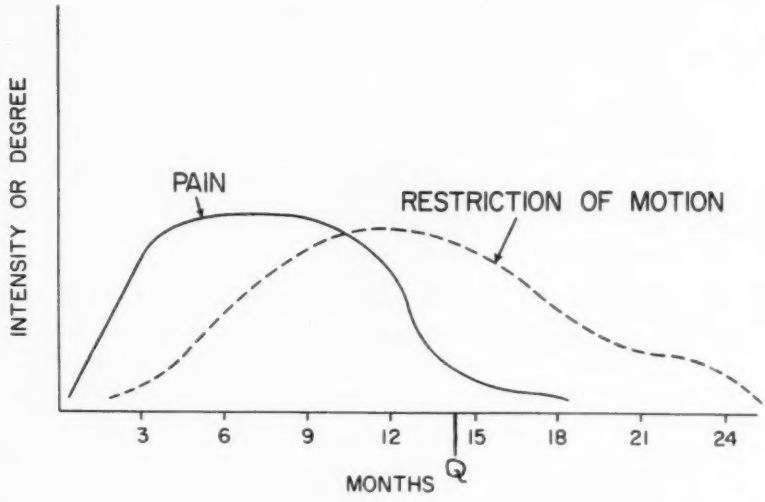

Fig. 1—Relationships of motion restriction and pain generalized for a frozen shoulder.

Significant shoulder trauma may not be recalled, but this entity may follow other upper extremity injury such as a Colles' fracture.

In some cases there may be a history of a previous acute or subacute inflammatory episode which had been ascribed to a bursitis. The acute episode was then gradually replaced by the clinical picture of a frozen shoulder.

The condition is usually two or three months old before the patient is seen by an orthopedic surgeon.

The patient is almost always more than 30 years of age.

There is some atrophy about the shoulder. Early in the course of the condition discrete points of tenderness are usually not elicited.

X-rays of the shoulder are often negative, though in some cases calcification at the insertion of the rotator cuff may be present. The laboratory findings are within normal limits.

This particular type of joint involvement is peculiar to the shoulder.

The general course of the disease follows the pattern shown in Figure 1.

Before going further, some terms require definition. The first is shoulder motion. Shoulder motion occurs at two major sites — the

glenohumeral joint and between the scapula and thorax. The acromioclavicular and sternoclavicular joints permit scapulothoracic motion. When an arm is abducted, motion takes place at the glenohumeral joint and then in the scapulothoracic area. The joint participation in movement can be simplified by stating that abduction, up to 60 degrees, is a glenohumeral function. Past this point the movement is increasingly scapulothoracic. When a frozen shoulder is at its worst there is restriction of both motions.

The next terms are rest pain and motion pain. We believe rest pain in this condition indicates an inflamed nerve segment, the result of an entrapment neuropathy. Although motion will cause mechanical irritation of the nerve segment and produce pain, immobilization does not relieve this pain as it will for the pain initiated by inflamed ligament, tendon or joint structures. These can cause motion pain. In the active phase of a frozen shoulder, both types of pain are present.

The difficulty in defining and treating the condition is a reflection of the lack of appreciation that two entities are present, one concerned with rest pain associated with alteration in scapulothoracic motion, and the other concerned with motion pain and associated with restriction of glenohumeral movement. Either entity may vary in intensity or be in a different position with relation to its time curve. The two elements that compose a frozen shoulder are presented below.

Scapulothoracic Restriction—Rest Pain

It has been demonstrated that rest pain in this condition is associated with an entrapment neuropathy of the suprascapular nerve as it passes through the suprascapular foramen[1, 2]. The suprascapular nerve is derived from the upper trunk of the brachial plexus. It runs downward and backward to reach the posterior aspect of the scapula by passing through the suprascapular notch. The notch is converted into a foramen by the superior transverse scapular ligament. The suprascapular nerve is a motor nerve, that is, it has no skin representation and carries only deep tissue sensation. It innervates the supraspinatus and infraspinatus muscles and portions of the shoulder and acromioclavicular joints. Pain resulting from irritation of this nerve is deep, and poorly localized. It is greatest at the posterolateral aspect of the shoulder.

The edges of the foramen are sharp and unyielding, compared to the nerve trunk. The margin for passage of the nerve is not large.

Motion of the scapula, carrying the foramen, may be likened to moving a ring along a slack string which represents the nerve. At the extremes of motion the nerve is taut. One particular motion renders the nerve taut and kinks it over a foramen edge—that is, cross-body adduction of the humerus with forward and medial protusion of the scapula. If the nerve is inflamed, this motion will increase the process by mechanical irritation.

If there is restriction of glenohumeral motion, forcing the desired range of arm motion will demand a greater excursion of the scapula. This increases the possibility of mechanical irritation of the suprascapular nerve by the foramen edges.

Once a neuropathy has occurred, either by a single severe trauma or repeated small injuries, there will be restriction of scapulothoracic motion on a voluntary basis. This restriction will disappear under anaesthesia, general or local. A block with a local anaesthetic will abolish pain arising from the neuropathy area and from the more distal areas of the nerve supply. Infiltration of the nerve segment with hydrocortisone will relieve only the pain caused by nerve inflammation, as hydrocortisone has no appreciable local anaesthetic property. These two substances offer a means of elucidation of the origin of pain.

Figure 2 shows the influence of scapular motion, in this case cross-body adduction, on the tension and course of the suprascapular nerve.

Glenohumeral Restriction—Motion Pain

Normal motion at joints requires two things—a stable hinge mechanism at which the motion occurs, and motor forces. The greater majority of joints require more than the joint capsule and associated ligaments for the hinge stability or fulcrum establishment. In the shoulder, as in most large joints, stability is also insured by musculature. Most of the common painful shoulder difficulties are caused by derangement of the muscular and ligamentous apparatus responsible for the retention of the humeral head against the glenoid. Any portion of the rotator cuff insertion or coracoacromial ligament may be the site of an inflammatory process. A non-specific connective tissue inflammatory process occurs in the shoulder which may or may not be associated with ectopic calcification. The same process occurs elsewhere in the musculoskeletal system at various tendon or ligament insertions with much less frequency. In addition, an almost asymptomatic calcification can occur

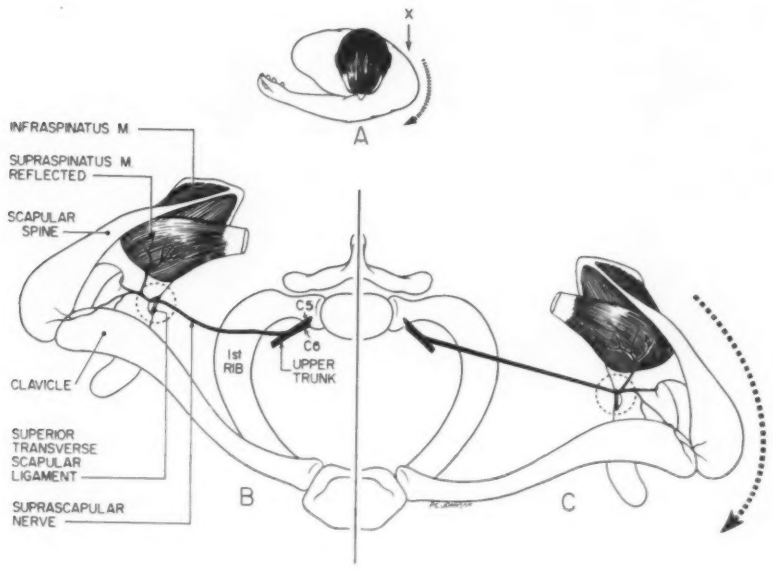

Fig. 2—Coronal view of relationship of suprascapular nerve. B is normal anatomical position; C depicts nerve tension produced by arm posture as shown by arrow in A. (Figures 1 and 2 reproduced by permission of *Surg. Gynec. Obstet. 109*:92-96, 1959.)

concomitantly with degeneration of the intrinsic tendon structure, brought about by aging and wear.

The acute phase of this inflammatory condition, generally called a bursitis, which responds well to anti-inflammatory medication and immobilization, is of no concern here. It is the possible residuals of the acute inflammatory reaction, or of trauma both direct and indirect, that are important in causing limitation of glenohumeral motion.

We have been impressed by the importance of the coracoacromial ligament[3] in causing restriction of glenohumeral motion in the majority of the disabled shoulders. A point of tenderness immediately lateral to the coracoid process is a consistent finding in most frozen shoulders which still show impaired function. This is the area of attachment of the coracoacromial ligament. The shape and character of this ligament is usually not well depicted in texts. It is a tough band which stretches from the coracoid process to the tip of the acromion. In life and in cadaver specimens, the band is bulged upward by the humeral head

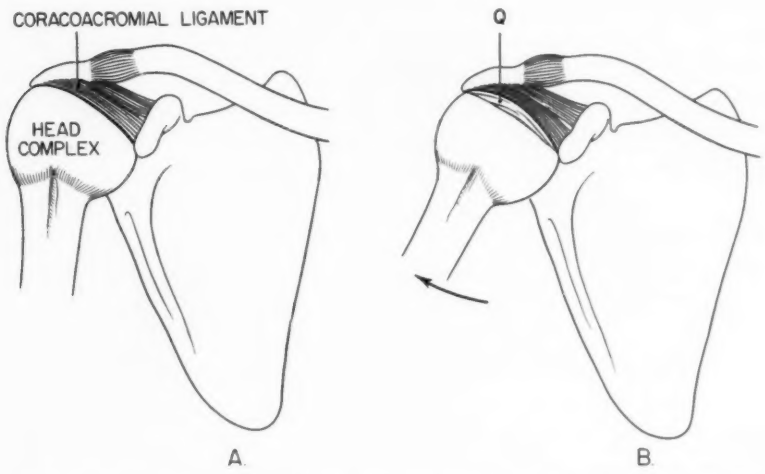

Fig. 3—Diagram of coracoacromial ligament and head complex (head complex—tendons of supraspinatus, infraspinatus, and teres minor covering and blending into capsule).

A. Normal anatomical position.

B. Impingement of head complex against ligament (Q) on motion.

with its covering of capsule and rotator cuff insertions (supraspinatus, infraspinatus and teres minor). One gets the impression that if the humeral head were removed, the ligament would subtend the acromial arch in a straight line, the chord of a circle. The compound curve, convex superiorly and anteriorly, which it assumes *in situ*, is not inherent in the ligament but is, as noted above, a function of head pressure. The head complex must slip against this ligament. Any loss of the ability of the head complex to slip by the ligament will lead to wrinkling of the underlying soft tissues.

It is easy to traumatize the tissues intervening between the humeral head and the ligament by an upward, medial or forward directed force. Any irregularities or thickening of the immediately underlying rotator cuff will impinge on the ligament. The resulting ligament irritation can lead to inflammation which will have a marked binding effect on motions of the humeral head, with subsequent secondary contracture. Early in the course of our investigation, we thought that the point of tenderness might be attributable to an inflammation of the coracohumeral ligament or a tenosynovitis of the biceps tendon. However,

subsequent dissections failed to substantiate a significant motion-blocking role to either of these two structures. Nor can we ascribe significance to the terms often used to describe this condition, i.e., pericapsulitis, or adhesive peri-arthritis, as primary effects.

Mechanical irritation of the ligament by movement of the humeral head with its overlying structures will cause motion pain. The innervation of the ligament is by the medial anterior thoracic and musculocutaneous nerves. This accounts for some of the referred pain pattern found in a frozen shoulder.

Figure 3 shows the relationship of the coracoacromial ligament to the humeral head complex.

Discussion

The basis for the earlier statement that this type of joint involvement is peculiar to the shoulder resides in the mechanical fallibility of two extra-articular factors. One factor is the derangement of glenohumeral motion, most commonly brought about by mechanical interference of the gliding of the humeral head complex under the coracoacromial ligament. The other factor is the vulnerability to trauma of the suprascapular nerve by the edges of its foramen, because of abnormal motion of the scapula.

While some cases of frozen shoulder arrive full-blown, without a good clue as to their origin or development, in most of them a careful history discloses either the initiation or the relationship of the factors. These follow several patterns:

A. Trauma to the shoulder which causes the scapula and humeral head to be driven forward, upward and medially. This force direction can cause trauma to both the suprascapular nerve and the ligament by jamming the rotator cuff between the humeral head and coracoacromial ligament. The injury may result from force applied directly to the shoulder, or from a distance. An example of the latter is the shoulder strain that results from the follow-through of the upper arm at the time a Colles' fracture occurs.

In this group there is the concurrent nerve and ligament lesion which can progress further through the entire course of a frozen shoulder.

B. Residuals of an inflammatory process, with or without calcification, or residuals of trauma to tendons or bone which cause restriction of glenohumeral motion, chiefly through impingement of the distorted structures on the coracoacromial ligament. As mentioned earlier, though other structural causes may be at fault, we believe this mechanism, implicating the coracoacromial ligament, is responsible in the majority of cases. The restricted glenohumeral motion forces a wider range of scapulothoracic motion to achieve desired arm movement. The increased scapular motion can bring about mechanical irritation of the suprascapular nerve, which will result in an entrapment neuropathy. The compensatory scapular excursion may come about through the individual's voluntary actions or even through external manipulation for therapeutic reasons.

C. There is a group that have sustained an entrapment neuropathy of the suprascapular nerve with little if any restriction of glenohumeral motion. This may come about through occult trauma. In this latter group are the effects of abnormal posture, as for example, the position assumed by the shoulder girdle in a hemiplegia. One shoulder girdle motion has particular significance for trauma to the nerve by the edges of the suprascapular foramen. The motion is lateral and forward displacement of the scapula. This occurs in cross-body adduction of the arm. A good example of this is the position of the left arm at the beginning of a golf drive.

Having seen the relationship that exists between the factors and the curve in Figure 1, we can account for the difficulty of evaluating previous treatment programs. Most previous treatments have had as a basis the notion that an increase in glenohumeral motion will decrease pain, and they have attempted to accomplish this by some type of manipulation, surgical lysis, or local applications of energy forms. It will be seen that in form A a lysing procedure will produce relief at point Q (Figure 1) when the entrapment neuropathy has run its course. A great many entrapment neuropathies become relatively asymptomatic in about twelve months.

In form B, lysing procedures (glenohumeral) will be effective if done before compensatory scapular motion has caused an entrapment

phenomenon incapable of spontaneous resolution. If glenohumeral lysis is successful, but the entrapment neuropathy is still active, rest pain and protective inhibition of scapular motion will continue.

In form C, which is basically a pure entrapment neuropathy, treatment, to be of value, must relieve the neuropathy.

Conclusion

The frozen shoulder is a syndrome which can be defined by the clinical features noted at the beginning of this paper. The chief elements are pain, both at rest and on movement, and restriction of motion. Both glenohumeral and scapulothoracic motions are limited. Rest pain is associated with alteration of scapulothoracic motion; and movement pain with restriction of glenohumeral motion. These two factors, which are combined in the frozen shoulder syndome, may exist in differing proportions and in varying degrees because of time relationships. This fact, of two separate variables composing one condition, each having its own rate or progress, has led to difficulties in defining the condition and evaluation of the various forms of treatment.

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PRACTICAL APPLICATION OF RADIOACTIVE METALS

*Transcription of a Panel Meeting**

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MODERATOR LEE E. FARR: Some years ago, at the end of the war, publicity in connection with radioactive isotopes and the newer devices of nuclear physics indicated that inherent in these agents lay great promise in resolving problems of diagnosis and therapy in medicine. A wave of optimism swept over the profession and many believed that advances would be exceedingly rapid and perhaps might lead to a repetition of events similar to the conquest of infectious disease achieved by sulfonamides and antibiotics in the preceding 15 years. However, as time has passed, it has become increasingly apparent that while the promise of usefulness of radioactive isotopes in the field of medicine is no less than it was in 1945 and '46, the problems in actually developing and adapting these materials to the point where they can be widely used are far more complex than was originally anticipated. Nevertheless, at the present time, in certain areas of medicine in both diagnosis and therapy, the use of radioactive isotopes has won a place as the procedure of choice under certain conditions. This is particularly noteworthy in the management and treatment of thyroid disease but isotopes are being used increasingly in the treatment of other illnesses and specific disorders as the profession becomes familiar with the possibilities inherent in these substances and the precise manner in which they must be used.

This afternoon I have asked our four distinguished guests to present first the broad aspects of the general area of the subject most familiar to them, speaking as much as possible from their individual experiences. As the discussion progresses I believe it will become apparent that we are dealing with general principles and that as these principles emerge clearly, not only the usefulness and advantages but also the disadvantages of radioisotopes in medicine will become much clearer to you.

Dr. Laszlo will discuss his experiences with the use of certain radioactive isotopes in the control of malignant disease and Dr. Cotzias will tell us some of his experiences in this field, particularly in relation to results which may be anticipated in the not too distant future.

Our first speaker will be Dr. Stuart W. Lippincott, who will discuss the effects of radioactive isotopes on tissues, and the kinds of changes one might expect to find.

DR. STUART W. LIPPINCOTT: Since all of you are familiar with x-radiation and gamma radiation in human beings, I shall confine my remarks to what takes place in tissues when doses of alpha and beta particle radiation are given and this will appropriately include a correlation of

the physiological and pathological in the thyroid of the rat. The rat has been selected as the animal for experimental study because of its small thyroid and its suitability for experimental work.

The isotopes to be considered are, first, I^{132}, a beta emitter with a half-life of 2.3 hours, and Astatine^{211}, an alpha emitter, with a half-life of 7.3 hours. These are two isotopes with short half-lives. They go very avidly to the thyroid gland and they can be studied quite readily in comparative doses.

(Slide) The first slide demonstrates the appearance of the normal thyroid in the rat. As in man, it has two major lobes and an isthmus.

(Slide) The next slide, under a higher magnification, demonstrates one observation important for comparative purposes, namely, that all of the acinar structures are closely packed together. This snugness allows for only a small amount of intervening connective tissue, but it does allow for capillaries, so that there is a good circulation in the gland itself.

(Slide) This demonstrates how the alpha track appears in the normal thyroid in the rat. Observe the short crisp black lines. They represent the alpha particles and they compose a compact track because this is a densely ionizing particle. The distance traversed by this release of energy is approximately 8 to 12 microns.

(Slide) The next slide shows the audiograph of the beta particle. One is impressed that only pinpoint dots are seen, not tracks. The reason for this is that now a weakly ionizing radiation is being dealt with in contrast to the strongly ionizing radiation of the alpha particle.

(Slide) In setting up the experiments we decided that we would try to grade the pathological anatomical results by starting with a low dosage, which would perhaps result in an entirely normal gland. That would be grade zero. If there was edema of the stroma only, that would be grade one. In grade two the effects would be more pronounced, with edema of the stroma and early evidence of epithelial degeneration in the acini. Grade three,—marked acinar necrosis peripherally, and grade four,—complete acinar necrosis.

(Slide) This is an example of what happens when about 15,000 rep* of I^{132} was administered. Note that the acini are still quite intact. The epithelial cells are in single layers and are perfectly normal but the snug arrangement with the acini back-to-back is no longer found—they are now widely separated. This represents the edema which has taken place.

* Roentgen equivalent physical.

(Slide) This slide, also under a higher power, demonstrates that this edematous area has released within it a fibrinous material which represents serum protein, so at these doses the first result is a physiological one. The acinar epithelium is spared and we have a release of serum protein through the small vessels.

(Slide) A level of approximately 100,000 rep has now been reached. Observe that the parathyroid is quite normal, that at the periphery there is a perfectly intact rim of thyroid acini and that the entire central part of the gland is completely necrotic.

(Slide) In this slide will be seen comparisons, at a slightly higher dose but in the same range, of what occurs when the alpha particle is given in the form of Astatine^{211}. Again this sparing action of the parathyroid is seen and we now have a complete obliteration or wiping out of all of the epithelial structures. So, by determining the dose, we are able to decide how much of the gland we shall render functionless and how much will remain intact, or, if we wish to render it completely functionless, we may accomplish it in this manner with alpha particle radiation.

(Slide) The final slide correlates the results between all of the dosages given. For example, two determinations can be made by giving these animals a tracer dose of I^{131}. We can find out what the physiological effect is upon the uptake of this isotope, and at the same time that we sacrifice comparative animals, we can determine what the pathologic changes are in the tissue itself. When we are working at a level of 15 to 30,000 rep, we have an inhibition of uptake ranging between 6 and 30 per cent and most of the glands are essentially normal. It is only when we increase the dosage to about 30,000 rep that we begin to see this physiologic change taking place in the stroma as a result of the effect upon the vasculature. As dosage is further increased to 60,000 and 70,000 rep, there is a tremendous inhibition of uptake of I^{131}. On reaching the maximum dose, resulting in complete obliteration, there is physiologically 100 per cent inhibition of uptake with complete loss of functional epithelial tissue. As we progress from grade zero to grade four, and as we progress from 15,000 to 140,000 rep, there is considerable uniformity in comparing the physiological and the pathological results. This leads us to believe that, fundamentally, we do not have a *qualitative* change resulting from differences in quality of ionizing radiation but do have a fairly clearcut correlation related to *quantitative* phenomena. In other words, the anatomical result is related to the *amount*

of energy which has been delivered to the target by the design of the experiment.

MODERATOR FARR: You have heard how time has become a factor in the use of this new modality, and its importance in the therapeutic usefulness of radioactive isotopes will be further brought out and developed by our next speaker, Dr. Victor P. Bond.

DR. VICTOR P. BOND: The degree of usefulness of isotopes, certainly in therapy and to a large degree in diagnosis, is determined either directly or indirectly by considerations of dosage. That is, those physical properties inherent in the isotope determine the amount of dose, its location in the tissues and the time at which this dose is applied.

I should like to consider primarily the problems and difficulties associated with dosage which are encountered in therapy with isotopes, although the considerations will apply, to a degree, to diagnosis as well. The difficulties we encounter are real and they are formidable. Only by recognizing and facing these problems can we approach the problem rationally and with any hope of success. In considering cure, the problem is more serious than it is in a consideration of palliation.

As you well know, isotopes in medicine are not new. In therapy they are not new. Radium has been used for more than 50 years. This brings us immediately to a consideration of the chief physical properties of isotopes that make them useful in therapy. As you also know, most isotopes used give off beta and/or gamma radiation. Some of the elements of high Z number give off alpha particles. Alpha particles penetrate tissue in the order of only a few microns, beta rays in the order of a few millimeters, gamma rays many centimeters. Each isotope has its own characteristic half-life which determines the dose rate.

Now to return to radium. It has been used principally in the form of needles and a grid pattern has been laid down in the tissue of interest. The beta and alpha radiations are shielded out. These are unwanted because of undesirable local necrosis, and the gamma radiation is used in a crossfire technique. The objective, of course, is the same as with external radiotherapy. What we are trying to do is deliver a maximum dose to tumor or involved tissue with minimal involvement of the adjacent normal tissue at the same time. With radium, the needles are removed after therapy because of the cost and scarcity of the radioactive material. Also, radium has a very long half-life. If the needles were not removed it would be like placing the patient under an x-ray

beam for the remainder of his life.

With the advent of the short-lived isotopes, cheap isotopes in large quantity, new vistas were opened, as has been mentioned by Dr. Farr. It is now possible to place isotopes in tissue and leave them in position, with no need to remove them. It is also possible to localize isotopes to a degree in various tissues, principally by two mechanisms. One is physiological, such as iodine to the thyroid, P^{32} to the bone marrow and certain colloids which can be used for localization.

Another means of approach is the infiltrative technique, the interstitial application, in which colloids of isotopes are usually injected directly into the tissue involved. However the application is done, we have, in theory, an ideal situation. There are millions of point sources within the tumor tissue. Irradiation is from within, not from the outside. It is not necessary to penetrate normal tissue, and beta or alpha radiation can be used for precise localization to that region where dosage is desired. It is *theoretically* possible, then, to achieve the ultimate in radiotherapy, that is, maximum dose to the tumor tissue and an absolute minimum to the adjacent normal tissue. Practically, it has not worked out quite as satisfactorily, and the reasons are largely because of dosimetric difficulties. This can best be illustrated if we return to the slides shown by Dr. Lippincott.

(Slide) The first slide illustrates well the principles I want to bring out, showing Astatine, an alpha emitter in the thyroid. Here we have a normal thyroid and an ideal situation. The isotope has been localized by physiological means. There is essentially uniform distribution of isotope throughout the tissue, and in addition to uniform distribution of isotope there is a uniform distribution of dose in rep or rad,* and this is reflected in the uniform destruction of tissue which is seen here. Also note that the structures adjacent to the thyroid are not affected. This is very precise localization. With this sort of an arrangement an ideal therapeutic result should be assured if this were possible.

(Slide) Another slide, shown by Dr. Lippincott, demonstrates I^{132} in contrast to the Astatine. I^{132} is a beta and gamma emitter, and the slide illustrates several principles I wish to bring out. Here, as with Astatine, the distribution of isotope in the tissue is uniform. However, the radiation dose at the edges falls off because of geometric considera-

* A unit of measurement of the absorbed dose of ionizing radiation. It corresponds to an energy transfer of 100 ergs per gram of irradiated object (including tissues).

tions. As a matter of fact, the dose delivered at the edge is half of what it is in the center. Thus, if we wish to achieve uniform cancericidal dose to the tissue, the dose would have to be raised by a factor of two over the average dose to the tissue. This is true of larger tissues not confined to the rat. It has been well demonstrated in the dog thyroid, for instance. Here again, with the beta radiation, little effect is seen beyond the confines of the tissue in which we are interested. That is, we get precision with beta as well as with the alpha radiation. I^{131} is a beta and gamma emitter, which leads to the next point. Essentially all of the dose to the tissue in question, the thyroid, has been delivered by the beta radiation. The gamma radiation, far more penetrating, escapes into the adjacent tissue—irradiates the adjacent normal tissue. However, the dose to the adjacent normal tissue is much less than to the localized area where the beta radiation is present. This consideration would also apply to intracavitary therapy where a gamma and beta emitter is in apposition to a surface. Most of the dose to that surface is delivered by the beta radiation, not by the penetrating gamma.

A last consideration has to do with very small lesions of the order of the size of the thyroid seen here. With the same isotope concentration in the tissue, the smaller the amount of tissue, the smaller the rep dose will be. This again follows from geometric considerations, and it means that for minute bits of tissue, for small metastases, to achieve the same radiation dose the isotope concentration must be raised above that for large tissues.

Now let us look at some specific approaches that have been used in isotope therapy and consider the properties that make the isotopes desirable or undesirable for the purpose at hand. Let us look first at examples of the physiological approach to the localization of the isotope. The most common one is iodine to the thyroid. Under these circumstances we must take the half-life into account. The localization of the isotope in the tissue involved must be very rapid or else the half-life must be relatively long. When these conditions are not met, excessive irradiation of normal tissues will result in the course of localization of isotope to the tissue being treated. Furthermore, by this means of localization, although superficially the distribution of isotope appears to be uniform, evidence obtained by radioautographs demonstrates that it is not. Actually, radioautographs of diseased thyroids indicate isotope dose variations within the tissues of as much as a factor of 20. Therefore

when isotopes, localized physiologically, are used in treatment, it is desirable to use either a very strong beta or a weak gamma emitter in order to irradiate the entire area in question and take care of the lack of uniformity of distribution of the isotope in the tissue. It might also be desirable to have an alpha emitter, if this is possible, to take care of the edge effects that were seen to be present in the thyroid tissue shown in the slide.

Another form of treatment is intracavitary therapy, mainly used to control effusions. For this it is usually desirable to have an element with a short half-life of the order of hours or a couple of days. It is advantageous to have a strong beta emitter that will penetrate the usually thickened serous membranes lining the cavities to be treated. It would be helpful if the emitter were a pure beta emitter with no gamma rays. Perhaps this requires some elaboration. As we stated, the total dose to the membrane to be treated is supplied primarily by the beta radiation. The gamma radiation in a mixed beta-gamma field contributes very little to the total dose. However, if a large dose of isotope is administered—of the order of 100 millicuries, which is not uncommon—the beta radiation dose to the membranes becomes quite large, of the order of 10 to 20,000 rep. It does not take a very high percentage of that to produce a sizable gamma dose, and this will irradiate large volumes of the adjacent normal tissue. That this actually happens, is evidenced by the fact that nausea and vomiting are side effects in this type of therapy and other gastrointestinal symptoms have also been observed. Therefore, a gamma emitter is not indicated for this type of therapy, or, shall we say, is not the most desirable. In addition, it is necessary that the isotope remain where it is placed. This is usually accomplished by putting the isotope in the form of a colloid that remains essentially where it is placed.

(Slide) We shall compare the properties of three isotopes that have been used fairly often for this type of therapy. Au^{198} has been used very commonly. It has a suitable half-life. The beta energy is approximately 1 mev.* However, it does have a gamma ray. P^{32} has also been used for this purpose. Its half-life approaches the undesirable level and the beta energy is greater than that of gold and no gamma radiation is present. In this same category I would also place yttrium which, like phosphorus, has the advantage of having no gamma radiation. It also has a desirable half-life and has the highest beta energy of the three. These properties

* Million electron volts.

result in more penetrating radiation of the membranes in which we are interested. From the considerations discussed, yttrium would, in my opinion, be the most desirable isotope for this type of therapy and I believe Dr. Laszlo will tell you more about that in his presentation.

The third type of approach is the interstitial or infiltrative technique. If we are considering treatment of a primary tumor, it is necessary to have either a very strong beta, or preferably, a fairly weak gamma emitter, or perhaps a combination of the two. If we have only the beta emitter, very precise and uniform localization of the isotope is then necessary if radiation of all of the involved tissue is to be accomplished. A miss of only a millimeter means a difference between a large dose and essentially no dose at all, as illustrated in the slides depicting the pathology in the thyroid gland. Again, it might be desirable if an alpha emitter could be used to take care of the edge effects that were noted in the thyroid. Here also it is preferred that the half-life be reasonably short.

In dealing with metastases from the primary tumor, the desirable attributes of the isotope to be used are somewhat different. At this point I should say that it has been established that colloids with radioactive materials do follow the lymph channels to the metastatic cells. For these metastases it would be better to use a weaker beta emitter than the one used for the primary tumor, although in such a situation an alpha emitter might be most advisable. As indicated before, it would be necessary to have a higher concentration of isotope in the metastases than in the primary, if metastases are small, to achieve the same rep dose. With the metastases the half-life should be reasonably long, since we do not wish excessive decay to occur while the isotope is in transit from the site of injection to the metastasis.

We have discussed only a few of the considerations connected with isotope therapy. My chief concern is for a realistic approach in such therapy; I do not wish to appear either overly pessimistic or too optimistic in evaluating the outcome of these approaches. It has been demonstrated to my satisfaction that in the internal usage of isotopes, as described, we have a precision instrument calculated to direct and localize radiation within an exact and circumscribed area. However, the very preciseness of the instrument can have an adverse practical effect in that the results are somewhat analogous to those obtained with the use of the high energy beams of teleroentgentherapy. However, it is

not possible to achieve that precision in location of the tumor and localization of its extensions. For this reason, in many instances x-ray with its spray radiation may prove more effective than the more precise approaches. I should like to emphasize that in many cases the procedures used have been tried under conditions in which one might have predicted slight chances of success and under these circumstances, failure may have caused undue pessimism in general.

The approaches to the problem are by two routes. We might term one an engineering, the other a physiologic approach. We know that if we get sufficient dose to the tumor, we can kill it via the engineering approach. Any cell can be killed by large doses of radiation. But, as I said, we have a precision instrument and we must learn how to use such an instrument effectively. This is a problem in technique or engineering. Witness the highly skilled technique and engineering employed in perfecting thoracic and heart surgery before these were brought to their present degree of effectiveness. Only a small percentage of that amount of effort has been directed toward the approach to isotope therapy. It can almost be said that such therapy has not been given a fair trial.

In attempting to localize radiation by physiologic means, experimentation has been with only a small percentage of available isotopes. There remain many possibilities to be explored in this area.

In closing, I should like to cite a few examples of new therapeutic approaches now in use at Brookhaven Laboratory on which I believe later speakers will elaborate. The first is neutron capture therapy for brain tumor, in which B^{10}-enriched borax is given intravenously, with the region of the tumor subsequently irradiated in a thermal neutron beam. This new approach aids in localization of the isotope in question. Consideration has been given to the time relationships in the distribution of the element in the tissues as well as the dynamics of localization of isotope. Instead of beta and gamma, alpha radiation is used, which will, presumably, radiate all cells and take care of the edge effect.

As a third approach we mentioned that during the process of localization of isotopes to the desired organ or region, a dose of normal tissues inevitably results. This problem of unwanted dose to normal areas has been taken care of to a large degree with neutron-captive therapy by injecting the material directly into the artery that supplies the area in question.

Finally I should like to mention intracellular irradiation as a new

and interesting approach now being used at Brookhaven. This is done by means of thymidine labeled with tritium, a very weak beta emitter. The thymidine goes to the DNA (desoxyribonucleic acid) in the nucleus of the cell, and the uptake by DNA is greatest in the more rapidly proliferating tissues. With this approach, the dose required to kill the nucleus is only a small fraction of the dose which is necessary to kill if the isotope is distributed at random throughout the medium and the cells. This is a most interesting and promising approach and the results obtained should be followed with great interest.

MODERATOR FARR: You have heard how the utilization of radioactive isotopes in medicine is dependent to a great degree more upon the type and energy of radiation than upon the element concerned. Nevertheless, the choice of the element concerned will largely determine the physiological performance of the isotope in question. Thus it becomes apparent that in most therapeutic procedures one may well be comparing beta effects with beta effects, or beta effects with alpha effects, and that these are really the important factors to be considered rather than whether element A or element B is used. However much we might like to generalize the problem there still remains the necessity for investigating each radioactive isotope in its own context. Today, with the possibility of manufacturing more than 700 different radioisotopes in a nuclear reactor, the staggering size of this task becomes apparent. I think we may perhaps be embarrassed by riches as much as anything. But a number of workers have persistently refused to be beguiled by this panoply and wide array of tools and have thoroughly investigated the usefulness and effects of preparations which, on theoretical grounds, should offer quick promise in the control of malignancies. Our next speaker, Dr. Daniel Laszlo, has had extensive experience in attempts to control and cure malignant disease by the use of radioactive isotopes, and he will now speak to you of these experiences in this promising field.

DR. DANIEL LASZLO: I would like to cover in the few minutes available to me a rather broad field. I would like to mention first that, compared to a few years ago, we now have considerable advantages. For example, compared to the time when only radium was available to us, radioisotopes are now widely used in research and therapy. There are three important types of applications. One is the topical application: for example, in the control of carcinoma of the cervix, radium is being replaced by radioisotopes which have more suitable radiation character-

istics than radium itself, more suitable both from the point of view of destroying the tumor and the protection of the normal tissues surrounding it.

As you have read in medical journals, hypophysectomy is now being done in an attempt to palliate certain malignant diseases such as cancer of the breast which has metastasized. There have been reports from Italy describing the interstitial instillation of a radioactive isotope, yttrium^{90}, into the pituitary with resulting complete destruction of the gland. This procedure is much simpler and safer than surgery, yet leaves the patient completely hypophysectomized. The palliative benefits observed were reported to be similar to those obtained by the surgical procedure.

Other advantages may also be gained by the interstitial application of isotopes, such as in the treatment of tumors of the prostate gland. Occasionally, this tumor causes great difficulties by obstructing the urinary tract and causes the patient a great deal of discomfort. It has been noted by a group of investigators that instillation of radiocolloids into the prostate gland can decrease the size of the tumor at the site of obstruction and thereby give the patient palliative benefits. For the treatment of a rare condition involving the urinary bladder, in which the entire internal surface is covered by multiple tumors, papillomatosis of the bladder, there was, up to the recent past, no satisfactory method of treatment available other than an attempt to remove surgically the entire bladder containing the tumor. In the past year several attempts have been made to fill the lumen of the urinary bladder with an isotope which would exert its radiation to the inner surface and thereby destroy the new growth. Several radioisotopes have been used. Some have been instilled directly into the bladder, others have been instilled into a rubber balloon which filled the bladder and the instilled material was left *in situ* for a certain period of time exerting its radiation to the tumor on the surface, and thereafter the material was removed. Favorable results have been obtained by this method of treatment.

As to the most common uses of radioisotopes in the palliative treatment of cancer patients, I might mention that three isotopes have been used for the control of cancerous effusions occurring in various body cavities, in the pleural or peritoneal cavities. The isotopes used are radiogold, chromic phosphate and yttrium.

The slides which I shall show point out the somewhat devious path-

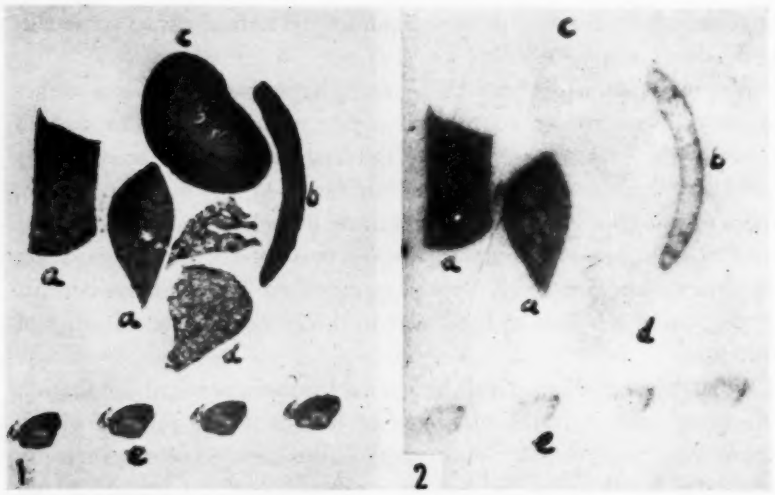

Fig. 1—Photomicrograph of organs of a mouse injected intravenously with $LaCl_3$ of 100 μc activity. The sections were taken 5 days after the injection and stained with hematoxylin and eosin. *a*=liver. *b*=spleen. *c*=kidney. *d*=lung. *e*=lymph node. *Figures 1, 2, 3, 5, 6 and 7 are reproduced by courtesy of the Journal of the National Cancer Institute.*

Fig. 2—Contact radioautograms of sections shown in Figure 1. Note heavy exposure from liver (*a*) and spleen (*b*), and light exposure from kidney (*c*) and lung (*d*). Note that one area of the lymph node shows a heavier exposure.

ways by which some of these isotopes can be developed and which may then ultimately find limited usefulness in therapy.

(Slide) I thought it might be of interest to you to see first these slides of mouse tissues. This animal received an isotope by intraperitoneal injection. You notice that these are liver and spleen slices. If the isotope is injected by the intravenous route the material is deposited in the liver and the spleen. It is of interest to note that if this same isotope is injected into the peritoneal cavity of an animal, then only the surface of the liver and spleen is coated. There is no activity in the interior of these organs (Figures 1 and 2).

(Slide) The next slide, also a radioautogram, is another illustration of these liver slices showing that only the surface of the liver is coated while the interior has no activity (Figure 3).

(Slide) This slide illustrates an interesting curiosity. This is the same

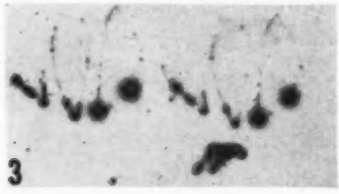

Fig. 3 Contact radioautogram of liver sections of a mouse injected intraperitoneally with radiolanthanum in the form of $LaCl_3$ of 100 μc activity. The animal was sacrificed 24 hours after the injection. Note that the radiolanthanum has coated the surface of the liver and that there is no uptake by the liver tissue.

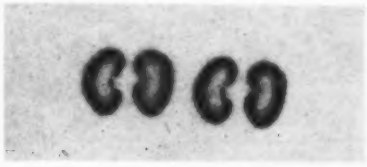

Fig. 4—Radioautogram of kidney of a normal mouse injected intravenously with Y—hydroxyethylaminodiacetate containing tracer doses of Y^{90}. Note the heavy concentration of Y^{90} in the cortical area. Radioautogram not enlarged. From "Distribution of Lanthanum and Yttrium in the Mammalian Organism", Proceedings of Symposium on Conference of "Rare Earths in Biochemical and Medical Research", Oak Ridge Institute of Nuclear Studies, G. C. Kyker, editor, published September 1956. *Reprinted with permission of the Institute.*

isotope seen on the two previous slides but the metal was injected intravenously in a chemical form which is selectively deposited in one part of the kidney, leaving most of the other tissues unaffected. This demonstrates that one can manipulate the conditions under which isotopes will find their way into certain specific organs or tissues at which one would like to aim the radiation (Figure 4).

In the first two slides (Figures 1 and 2), certain conditions were demonstrated under which it is possible to have the isotope deposited only on the surfaces of tissues. This would therefore be a suitable condition for the use of this isotope in the treatment of malignant effusions. In experimental animals, for instance in ascites tumor of the mouse, where the tumor is localized in the peritoneal cavity, we have noticed that when the yttrium isotope is injected into the peritoneal cavity there is good localization in the cavity and very little of the isotope is found in tissues other than in the injected area. Under these con-

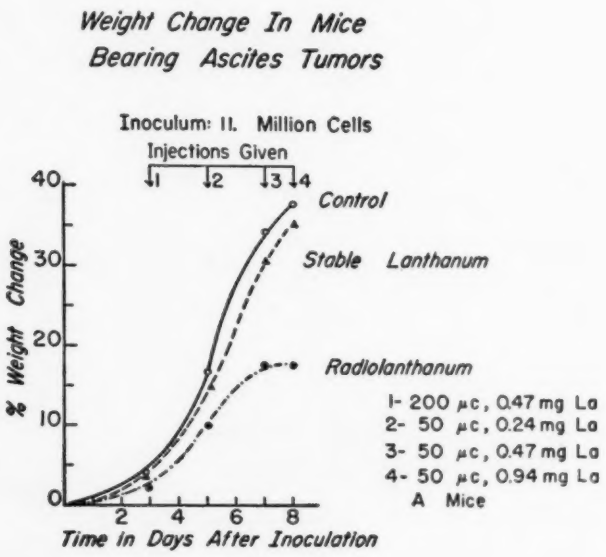
Weight Change In Mice
Bearing Ascites Tumors
Inoculum: 11. Million Cells
Injections Given
1
2
3
4
Control
Stable Lanthanum
Radiolanthanum
1- 200 μc, 0.47 mg La
2- 50 μc, 0.24 mg La
3- 50 μc, 0.47 mg La
4- 50 μc, 0.94 mg La
A Mice
% Weight Change
Time in Days After Inoculation

Fig. 5

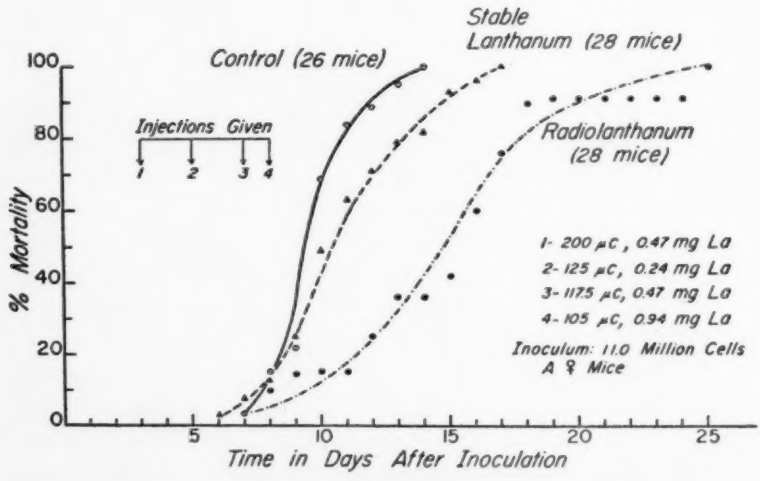
EFFECT OF STABLE AND RADIOLANTHANUM ON
SURVIVAL OF MICE BEARING ASCITES TUMORS
Stable
Lanthanum (28 mice)
Control (26 mice)
Injections Given
Radiolanthanum
(28 mice)
1- 200 μC, 0.47 mg La
2- 125 μC, 0.24 mg La
3- 1175 μC, 0.47 mg La
4- 105 μC, 0.94 mg La
Inoculum: 11.0 Million Cells
A ♀ Mice
% Mortality
Time in Days After Inoculation

Fig. 6

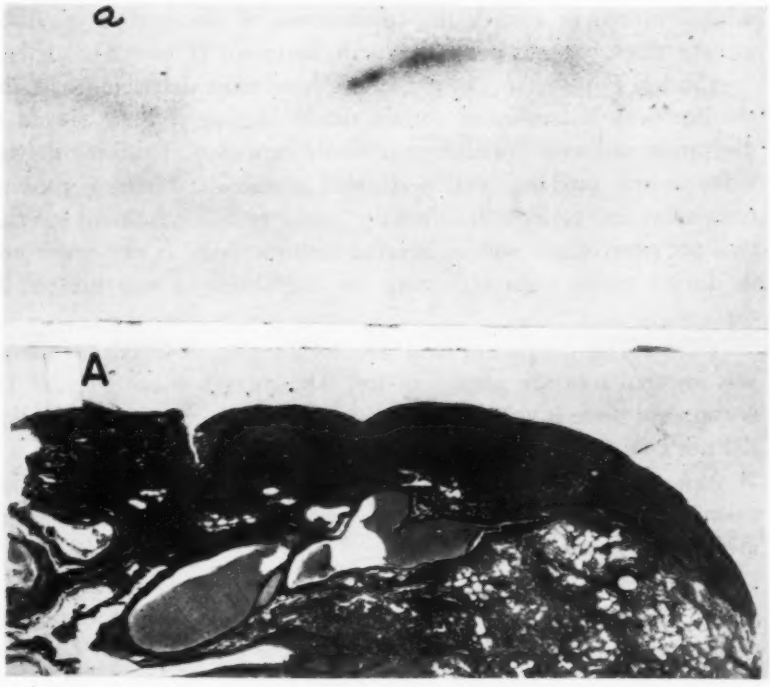

Fig. 7—Radioautogram 3*a*, and photomicrograph 3*A*, of lung. In this instance the whole paraffin block was placed against no-screen x-ray film. After 5 days' exposure the paraffin block was removed and a microtome section prepared.

ditions, less than one per cent of the isotope injected was found outside the cavity and taken up by other tissues. This is a rather safe percentage and would indicate that this may be a suitable form of therapy.

(Slide) In this case we have a follow-up demonstration to show that when such an isotope is injected into ascites tumor in mice, one is able to affect the growth rate of this tumor, i.e., to inhibit it. This growth curve differs from that of the control group and from that of the animals which received the stable component and not the isotopic chemical. This radioisotope has, therefore, an effect on the tumor with which it comes in contact (Figure 5).

(Slide) Here is a survival study of tumor-bearing animals. The animals of the control group succumbed at a faster rate, whereas the

animals which were injected with this isotope had a longer survival. This illustrates in animals the effectiveness of this isotope on tumor growth when brought in contact with the tumor (Figure 6).

(Slide) To use this isotope in man one must determine first that the isotope will localize in certain tissues because if there should be dissipation and wide distribution it would be useless. This slide shows a study in man similar to that performed in animals. The subjects were terminal cancer patients. It shows that under certain conditions less than two per cent of the isotope injected into the body cavity was found in distant parts, again indicating the usefulness of this isotope for therapy.

(Slide) This is a part of lung tissue of a patient in whom the isotope was injected into the pleural cavity. The surface is coated with the isotope and there is no activity in the interior. All this part of the lung did not contain activity (Figure 7).

When radioyttrium is instilled in the pleural cavity in certain calculated amounts, the radiation received by the surface of the pleura involved by tumor is satisfactory.

(Slide) The technique of intracavitary isotope administration is rather simple because this is a beta-emitting isotope. Therefore the protection required for the personnel and for the patient is less of a problem than if gamma rays were also being emitted by the isotope. We have a bottle protected by a plastic shield. Thoracentesis is performed first and approximately 100 ml. of pleural fluid is put into this bottle which contains the isotope. After the thoracentesis is completed, the bottle containing the mixture of isotope and pleural fluid is reversed and simply instilled through the same closed system into the pleural cavity (Figure 8).

While the procedure is simple, it is not easy to judge whether it will be effective, for it is most difficult to judge whether one really has accomplished what one set out to do. I should like to point out that in about half of the cases so treated, the results proved beneficial. In this series, 15 patients were treated, with a sufficiently long follow-up in 11. In seven patients results were satisfactory. In surveying the literature, it will be noted that whichever isotope is used for this purpose, whether gold or chromic phosphate or yttrium, temporary but significant palliative benefits can be obtained in approximately 50 per cent of the patients. From this point of view, the clinicians might consider radio-

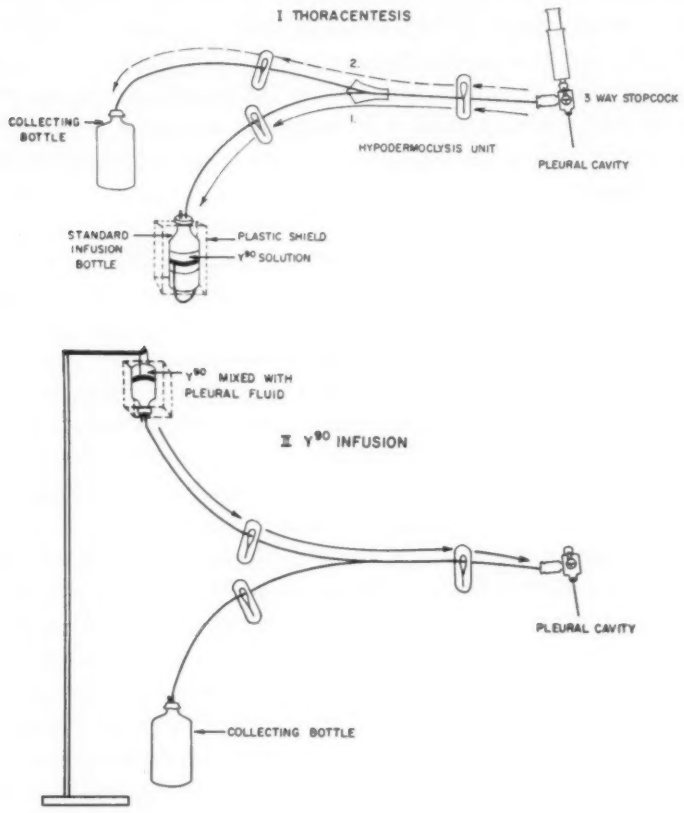

Fig. 8—Intracavitary administration of Y^{90}. First published in an article entitled "Radioyttrium (Y^{90}) for the Palliative Treatment of Effusions Due to Malignancy", by E. P. Siegel and others, in The Journal of the American Medical Association, June 9, 1956. Reprinted by permission of the authors and the Journal.

yttrium as a modality in the therapy of some of their patients with effusions caused by malignancy.

In summary then, I would conclude that with much work the fruits have been slight. However, I do believe it is reasonable to expect that with persistent work, additional benefits will be had.

MODERATOR FARR: In his discussion, Dr. Laszlo has emphasized the difficulty of evaluating the results of therapy in the complex field of management of malignant disease. It is obvious that a greater fund of

knowledge is needed regarding the biology of neoplastic disease to enable us to determine results of therapeutic procedures in cases in which a complete cure cannot be anticipated, particularly since there is no way to determine the potential life-expectancy of the patient. For proper evaluation of the success of therapy in neoplastic disease, it is necessary to have more precise physiological information based on the natural history of the disease.

Our next speaker, Dr. George C. Cotzias, has been concerned for the past few years with just such physiological problems which might lead to more precise localization of radioactive isotopes for therapeutic purposes resulting in a better understanding of the effects of radioactive isotopes should they contaminate body structures.

DR. GEORGE C. COTZIAS: I think that my role is to illustrate some of the points made by the previous speakers, because I can talk to you only about the development of a method, how this method for treatment produced a considerable amount of interest, how we were disappointed in it and then how we went back to retackle the problem.

I am going to talk to you principally on behalf of a group of isotopes now being neglected on the scientific scene. This is the group we refer to as the short-lived isotopes. They are being neglected because their availability is relatively limited and restricted to areas relatively near a reactor. We are blessed with such a reactor at Brookhaven and therefore this limitation is removed. In my opinion, the short-lived isotopes convey several benefits to the investigator and to the clinician. One is that they can deliver a high dose rate which may be analogous to the strong punch a boxer delivers to the chin, as opposed to a number of weaker punches delivered to the body.

The second benefit is that one does not have to be as concerned with personnel and safety factors with short-lived isotopes and there is also no disposal problem, because they themselves resolve these problems by disappearing from the scene. The one isotope with which we have had the most experience has been Mn^{56}, which is primarily an emitter of strong beta rays. It also emits some gamma rays and therefore is beneficial on two accounts: it can deliver a dose but it can also be monitored fairly effectively from the outside.

(Slide) The first slide demonstrates the sum total experience covering 19 cases. Trace doses were given which show only the whereabouts of this isotope. As you see, these are arbitrary units. This is due

to the fact that the surface of the body was monitored with a scanning device, while a different procedure is used for determining radioactivity in the blood. A mathematical trick of normalizing these two values has been used. This slide demonstrates first that the isotope has a shine. Its mere entrance into the room is registered by the counters which are placed over the thigh and the liver of the patient prior to the injection of the isotope. Above and beyond that, this slide shows that following the injection of the material there is a sudden appearance of the isotope in the blood and then a very profound and rapid disappearance which thereafter remains sustained. Concomitantly the liver area becomes and remains enriched for a period several times the half-life of the isotope. This brings us to the other counter which lies on the thigh. What this counter sees is not only what is in the thigh but also what is in other parts of the body. We have already shown you that a certain amount of shine is seen by this particular counter even when the isotope is brought into the room. This means that the relative position of these two lines should not be regarded too seriously. The existence of a large concentration in the liver, as will be shown later, tends to raise the value for the thigh. This type of technique does not permit one to get quantitative estimates to determine where the radioisotope goes. Therefore we had to rely on animal experimentation for this particular type of quantitative investigation.

(Slide) This shows that, indeed, an amount of radioactivity equivalent to 35 per cent of the injected dose can be found in the liver following injection. In this case the rat was studied. However, the same thing holds true in other species. The pancreas, which lies in the same area, contributes approximately 5 per cent to the total liver area dose. We know that the localization of the isotope in this area is intracellular, because we have recovered the radioactivity in association with an intracellular fraction of liver which is known as the mitochondria.

On the basis of these findings, namely, of a quick disappearance from the blood stream after injection and a fairly good enrichment of the liver, we thought we might benefit some liver-cancer patients by giving them an effective amount of radiation. We chose to give 300 to 400 millicuries of this Mn^{56} intravenously. This had been calculated to deliver of the order of 1200 rad to the liver and of the order of 75 rad to the rest of the body, which seemed to us like a good differential. This treatment was given in three cases. The first had a primary cancer of

the liver, histologically demonstrated, and the other two had secondary tumors of the liver, secondary to primary lesions in the colon. In the first case we observed that the size of the liver markedly diminished following the administration of this dosage. The hypoglycemic episodes which were characteristic of the patient's disease became considerably less frequent. His general status improved and we were indeed markedly encouraged. Concomitantly a battery of liver function tests proved no change in his liver condition, which was fair at the time of the administration of the isotope. The treatment did not seem either to improve or hinder the status of the liver function. In the other two cases we had similar but less encouraging results. The subjective findings and the diminution in liver size were quite unequivalent. However, in all of these three cases, at the end of approximately three weeks, the hematological signs characteristic of irradiation syndrome occurred. Depression of the platelets, depression of the lymphocytes, depression of the granulocytes and a little later the development of a slight or moderate anemia, are conditions which appeared in all three cases cited. These responded to classical therapy, primarily supportive. This experience demonstrated that if this approach were going to be useful, it had to be modified on the basis of the principles outlined to you by Dr. Bond.

The first effort was to keep the isotope away from healthy tissues as much as possible. The second, to deliver it to the disease-stricken target.

(Slide) In the series of efforts with the patients we had used the intravenous route of administration, already commented upon by Dr. Laszlo. What you see in this slide is that the liver contained a high concentration of isotope but that there was distribution of isotope in other organs. In our studies we found that there was some radioactivity located in the bone marrow also. In view of the fact that the same kinetics of disappearance from the blood occur, irrespective of what vein of the body was injected, we thought that it might also occur in the portal vein. This vein has similar characteristics in terms of mixing, as the other veins.

(Slide) A comparison of the intravenous route of administration with the intraportal is here illustrated. This also is an animal experiment with manganese^{56} injected intraportally. There is a considerable enrichment of the liver as compared to the intravenous injection. Furthermore, the bone marrow contains very small amounts of radioactivity

indeed. There is also a marked diminution in the amount of isotope that escapes into the periphery. By contrast, look at the data from the intravenously injected animals. Were it granted that this approach deserves further trial, and I believe it does, then it must also be granted that manganese is by no means the only isotope which should be used for this purpose. On the basis of what Drs. Laszlo and Bond have said, one might choose isotopes even better qualified than the one we have used. I have in mind a beta emitter, Zn^{65}. It is a short-lived isotope. It can deliver rapidly a large dose. Possibly with this procedure it might deliver it on target. The zinc isotope behaves very much like the manganese isotope in the experimental studies.

MODERATOR FARR: You have heard the panel members discuss some of the problems and present day uses of radioactive isotopes, as well as give a brief description of advances that may be realized in the near future.

A few questions have been submitted from the floor. The first is: "Please explain the method of annihilation radiation." Dr. Bond, will you take the question?

DR. BOND: Annihilation radiation results when a positive and a negative particle, the size of an electron, come together. The particles disintegrate and gamma rays are emitted. Gamma rays are emitted in opposite directions, and this process is used effectively, with coincidence counting, to localize tumors. Particularly, it has been used for brain tumor localization.

MODERATOR FARR: Does that answer the question? It is the union of positively and negatively charged electrons which results in their total destruction and their disintegration initiates the formation of gamma waves traveling in opposite directions. Since the *matter* has disappeared and *electromagnetic energy* has taken its place, the term "annihilation radiation" or "anil radiation" is used.

Dr. Laszlo is asked: "Would the isotope be of value in the management of ascites caused by liver cirrhosis?" The second part of that question is: "Are the patients who receive the isotopes dangerous to the surroundings, from the standpoint of radioactivity?"

DR. LASZLO: The first question is whether the isotopes would be useful in controlling fluid in ascites. We have no experience and so cannot answer. I don't know at the moment of any report in the literature on this aspect.

I should like to point out that we do not know the exact mechanism by which isotopes control fluid accumulation in tumor.

The second question is whether patients receiving isotopes present a threat to the surroundings, from the standpoint of radioactivity. In actual practice, they are rarely ever dangerous, but this would depend on the type of isotope used. With a beta-emitting isotope there would be no hazard to the surroundings since penetration of beta rays is very limited.

With an isotope emitting strong gamma rays there might be some slight danger, depending upon the dose used for the period of the half-life, or the period of activity, of this isotope. This would be another reason to prefer beta-emitting isotopes in topical therapy.

MODERATOR FARR: In general, I think one might say that an isotope which is not an extreme hazard to the individual in whose body it resides also presents no extreme hazard to those who may be responsible for the patient's care.

Here is another question for Dr. Bond: "Can all tumors really be destroyed if an adequate dose of radiation can be delivered to them?" Would you not rather try to potentiate the sensitivity with some agent?

In answer to that I would like to say we would like to try something!

DR. BOND: I base that statement, that it would be possible to destroy the tumors, on the well-known fact that if the dose is high enough any living matter can be destroyed. It is also well known that tumors that are accessible, for instance tumors on the skin, certainly can be effectively destroyed if the dose is high enough. So I think there is no doubt that tumor tissue can be destroyed. It would of course be highly desirable if methods were found to potentiate the action of radiation selectively upon the tumor and this approach is being vigorously investigated. A search is being made for chemical substances which will localize in tumor and which will potentiate the action of radiation.

Another approach that is being pursued extensively involves increasing the oxygen tension in the tumor. This is being done in England particularly. It is well known that increased oxygen tension potentiates the effect of radiation. This is being given clinical trial, and patients are being irradiated under conditions in which the entire patient is subjected to atmospheres of oxygen in excess of normal.

MODERATOR FARR: *As a pathologist, Dr. Lippincott is always skeptical. Would you like to comment on this question?*

DR. LIPPINCOTT: Yes. I think if you would broaden the term "potentiate" and say it would be desirable to use some normal or perhaps abnormal physiological mechanisms, there is also some hope here. For example, if one performs a complement-fixation test in an animal that has a neoplasm, such as a Brown-Pierce carcinoma in the rabbit or various kinds of carcinoma in man, and if the antigen is prepared from the tumor itself, one can demonstrate in the animal that the antibody or the reagin lies primarily in the gamma-2 globulin fraction. For that reason we have been tagging the gamma-2 globulin obtained from patients with neoplastic diseases. The attempt here is to be certain that when we introduce the normal globulin into the cancer patient we have no antibody reaction and a given turnover rate. In the second instance, we have antibody-antigen reaction, namely, the tumor and gamma-2 globulin with the antibody uniting. Then we have a different turnover rate. We have, then, in this instance made use of a physiological, abnormal physiological mechanism to drive the isotope to the target, and in our preliminary experiments we have seen some slight difference between the turnover of the normal gamma-2 globulin and the cancer-2 globulin. Therefore I would say that it would seem worth while to use these physiological mechanisms as aids in delivering the isotope to the desired target.

MODERATOR FARR: *I have another question regarding the carcinogenic properties of radioisotopes, that is radioactive I^{131} for hyperthyroidism, or follow-ups not of significant duration as yet. There is no question that radioactive isotopes are carcinogenic agents. In this they share a property with a wide variety of organic compounds. It is not unique for radioactive isotopes. Therefore, if one uses radioactive isotopes it is always necessary to set up proper observation so that one can ultimately tell some 20-30 years later what may be the somatic effects which may result in malignancy in patients so treated. As far as I am aware, no one to date who has been treated for hyperthyroidism with radioactive I^{131} has developed carcinoma of the thyroid. Are any members of the panel aware of any such reports?*

DR. LIPPINCOTT: Dr. Klanman reported in his review in *Medicine*, about a year and one-half ago (1956), that in their extensive experience at the Massachusetts General Hospital there was no proven case. Subsequently, at a conference about a year ago, attended by many people who had participated in this type of work, he further stated that he

still believed there were no cases resulting from the administration of I^{131} for hyperthyroidism.

MODERATOR FARR: There are very few individuals who have been heavily treated for metastatic cancer of the thyroid who subsequently developed leukemia after receiving over a curie radioactive iodine. Whether this is cause and effect, I leave to you to judge. There have been, in some instances, high doses over five or six years, for the treatment of a primary malignancy, followed by leukemia.

Dr. Cotzias, what is the possible effect of accumulation of Mn^{56}? What role does the reticuloendothelial system play in this?

DR. COTZIAS: In my opinion the reticulo system does not play any role in this which can be demonstrated by any measurements we have set up. We find the isotope is picked up. As a matter of fact, this type of question has led to a rather interesting study, interesting from the physiological point of view, if not from the subject matter of this meeting. We were struck also by the fact that the liver, the pancreas, the kidney, the spleen pick up manganese. As you remember from your histology lectures, every time the professor of histology wanted to show you mitochondria he used tissue from the liver or pancreas. This suggested the notion that the mitochondria in the tissues probably soak up the manganese isotope. This was experimentally confirmed. The mitochondria are located within the hepatic cell. As you know, the reticuloendothelial apparatus is different from the hepatic cell. Therefore we cannot tell whether or not the reticuloendothelial system is involved in rapid transit. We know that within ten minutes of injection of the isotope we recover the isotope in the mitochondrial fraction of liver, brain or kidney.

MODERATOR FARR: *I have another question. "Could you explain the neutron capture theory in the treatment of brain tumors?"*

Perhaps I should try to answer that one myself. The neutron capture hypothesis requires the use of an element of high cross-section capture for thermal neutrons in relation to the elements in tissues. This is physical jargon for saying there is good likelihood that the action that one desires will occur in the target atom rather than tissue atoms. The thermal neutron has an energy of 0.02 electron volts. Some atoms have the capacity readily to capture or incorporate thermal neutrons within their nuclei. When that is done, in a few instances the atom involved is then changed to an excited form which may disintegrate in a variety of

ways. If it be uranium, it disintegrates into two heavy elements, which is indeed the reaction that occurs in the nuclear reactor. If, however, it be an atom of boron of mass 10, following capture of the thermal neutron, it becomes not a stable form of boron 11, which is the form of 80 per cent of all boron on the surface of the earth, but it becomes a very excited atom of boron 11 and almost instantaneously, within less than 1/1,000 of 1/1,000,000 of a second, it disintegrates into an alpha particle and a lithium particle, traveling in opposite directions. The total pathways traversed by the alpha particle and the lithium atom are approximately 1 cell diameter. Therefore if this reaction can be caused to occur within a malignant cell, the capacity exists to destroy that cell without causing any destruction or disturbance of surrounding cells. Then, if there be a difference in the rate of distribution of boron from the blood stream to or about a tumor cell as compared with the normal cell—and we know this rate—it then becomes possible to supply from an external source, namely a nuclear reactor, thermal neutrons at a time when the boron is accumulated in the tumorous tissue and before it has accumulated in the normal tissue. By the resulting capture reaction, theoretically, one can destroy the tumor without destroying the normal tissue. The chemical and physiological behavior of neoplasia themselves provide the selectivity desired for placement of the boron. The neutrons provided distribute themselves as, let us say, essentially a gas, so that we have no critical geometry to consider in the neoplastic region.

Thus, in theory, this is a very simple and effective way of treating a tumor. In practice it is complex and difficult. A great deal more work must be done before we can reach some reasonable assessment as to whether this can or cannot be accomplished on a practical basis.

We had originally planned to allow some time for a brief discussion of the radioactive fall-out problem. As we read about it today it is a problem with which the medical profession must be concerned, although it need not necessarily be a cause for alarm.

My oldest daughter is in the process of trying to decide what colleges to apply to for next year. I am concerned about her study of these colleges and her choice but I am not alarmed about them. The medical profession should be gravely concerned about the problem of fall-out but at the present time there is no evidence that it needs to be alarmed. This is not a new problem to the medical profession. It is essentially a restatement of many of the research, investigative, and clinical prob-

lems which the members of the panel have given you this afternoon. It is being brought to us under a new guise but it is essentially the same problem which has confronted us for a good many years. We have been concerned for many years with the problem of malignancy in miners of uranium ores, particularly in Europe. We have been concerned for a long period of time with the problem of radium, especially in industry, and about the advisability of permitting unrestricted sale of radium waters in the markets of the United States. These are problems identical to those presented by fall-out. Before we were aware of radioactive isotopes we were not concerned with a naturally occurring radioactive isotope in the body, K^{40}, but now that we are aware of it, it must be taken into account and included in any attempt to measure additional radioactivity that is used in the body. Thus we see we are dealing with an increment of radiation exposure. So, neither in terms of medicine nor in terms of physiology of the human body is the existence of radioactivity within our structures a novelty, or something new. But because it is present, it behooves us to be aware of it, to so condition our medical examinations that we will accumulate pertinent data of known exposure. If indeed at some time in the future a point may be reached in which the concentrations of these materials in the body may be of grave medical significance, then we shall be aware of it long before that time has arrived and take proper steps to prevent hazardous exposure.

The publications of the Joint Committee for Atomic Energy of the House of Representatives and the Senate are available from the Government Printing Office. They are two thick volumes in which exhaustive testimony is presented by scientists in all fields, by people from all areas affording us a complete summary of the data and information of knowledge, by those concerned with the fall-out problem. There is no better treatise on this particular subject than this publication. I commend it to you because it is necessary that members of the medical profession study reports such as this in which the fears of the geneticists are thoughtfully presented. The evidence to date, of physiological damage or its lack, is meticulously documented. The problem, of course, is the social evaluation and it is the responsibility of medicine to digest these data, then to come to a conclusion regarding the risk and hazard involved in this particular social endeavor of man, in terms of the life of each and every individual to come under the purview of the physician.

It is because of the lack of evaluation and summation of the evidence in this field by the medical profession that there has been so much public concern. This lack has also contributed to the prominence given many statements made by those who are not well qualified in the field of medicine but who, from their own point of view, see potential hazards existing in present practices. They feel, and rightly so, that they would be remiss if they did not bring these matters to the attention of the public. I believe that it is urgent that physicians become more thoroughly acquainted and reacquainted with the effects of radiation. As you listened to Dr. Lippincott today I am sure you all recall having these same facts available in medical school and it is now simply a matter of putting them into another context and evaluating them in terms of their true significance for mankind. As I say, it is not a new problem, but an old one, and as physicians we must readdress ourselves to this particular problem in its present-day context.

I wish to thank the members of the panel for their most interesting and stimulating discussions of a very difficult, complex field on the utilization of radioactive isotopes in the practice of medicine.

MEDICAL PRACTICE IN COLONIAL AMERICA*

JOHN RUSSELL TWISS

THE phase of American Medicine reviewed here covers the period extending from the time of the earliest settlers to the end of the 18th century. In general, the period of the 17th and 18th centuries was one of the most interesting and most important in *all* medical history; in this country, the advances were truly remarkable. Outstanding accomplishments included the formulation of some of the basic principles of diagnosis and therapy now in use and the establishment of early medical societies, publications, libraries, medical schools, hospitals and dispensaries. The great progress in America was based, in turn, upon the earlier development of European medicine and science, the results of which have been justifiably considered of fundamental importance in transforming medicine from the empirical stages of previous centuries to the rational approach of present-day methods[1].

This period of medical history was characterized by the development, in Great Britain and continental Europe, of many outstanding practitioners, surgeons, teachers and medical institutions of world-wide influence. Specifically, medical progress was greatly enhanced at that time by momentous discoveries and advancement in the basic sciences of philosophy, chemistry, biology, histology, embryology, pathology, anatomy and surgery[1]. While most of the advancement in medical knowledge originated in England or other European countries, many American physicians also made significant contributions to the natural sciences, such as botany and zoology[2, 3, 4].

THE EUROPEAN HERITAGE

Prior to the Revolutionary War, medical practice in this country was entirely dependent upon European and British medical education, particularly that furnished by the University of Edinburgh, which was founded in 1685. In fact, it was in Edinburgh that most of our leading

* Presented at a meeting of the Section on Historical and Cultural Medicine at The New York Academy of Medicine, January 28, 1959.

physicians of early colonial years were trained. The Universities of London, Paris, Rheims, Leyden, Vienna and Halle also provided training for some of our early physicians[3]. In this country, the first medical degree was conferred in 1770, by King's College, now the College of Physicians and Surgeons of Columbia University.

The preeminence of medical learning at the University of Edinburgh in the 18th century was the result of having a faculty trained in eminent European medical schools, some of which had been in existence for centuries. Among these was the Italian School of Salerno, "considered ancient in the year 846", which provided teaching in philosophy, theology, law and medicine. This school was also an outstanding medical center to which the great medical teachers had for centuries attracted students and patients from all parts of the then known world. Evidence of the thoroughness and proficiency of the medical practices taught at Salerno is still available in the *Regimen Sanitatis Salerni*[5]. This work, consisting of a series of instructions for patients after their discharge from the hospital, was originally written in Leonine Latin verse around the year 1130. Among the 240 subsequent editions, in many languages, is an admirable English translation published in 1607 by the poet Sir John Harington.

The important influence of events of the 17th and 18th centuries upon medicine and science can probably be best illustrated by mention of a few of the individuals responsible for cultural and scientific accomplishments of that period. Those were the times of such great men as Rembrandt, Rubens, Shakespeare, Milton, Molière, Bacon, Joseph Priestley and William Harvey. It also may be said that European medicine was benefited in that era by some of the greatest names in medical history. Among these were Thomas Sydenham (1624-69), Anton van Leeuwenhoek (1632-1729), Friedrich Hoffmann (1660-1742), Herman Boerhaave (1668-1738), William Heberden (1710-1801), William Cullen (1712-1790), William Hunter (1718-1783), John Hunter (1728-1793), William Withering (1741-1799), Edward Jenner (1749-1823), and the Munro family, three generations of which held the chair of Anatomy at the University of Edinburgh for 126 consecutive years.

In the field of medicine, important events included the development of the microscope and thermometer, Harvey's famous article on the circulation of the blood, which appeared in 1628, the demonstration and measurement of blood pressure by the Reverend Stephen Hales in 1711,

and the discovery of oxygen in 1764. Among other significant events in European medicine during that period were the published description of the radical resection of the breast for cancer in 1634, the intravenous use of drugs in 1656 by the architect, Sir Christopher Wren, the successful transfusion of sheep's blood into a human being in 1667, and the demonstration, in 1796, of the value of cow-pox vaccine for smallpox[3]. Also at that time, great universities were established, diseases were classified, large systems of medicine were published, the science of clinical pathology was founded by Morgagni, pharmacology made great strides, medical dispensaries and hospitals were founded and medical societies and medical periodicals began their existence[3].

Since medical practice up to the time of the American Revolutionary War seems to have followed closely the teachings of previous centuries, a review of the rationale of those practices is in order.

In the *Regimen Sanitatis Salerni*, previously mentioned as having been translated into English in 1607, are many remarkably sound ideas on health, hygiene, diet and medication, based on a program of "good humor, rest and sobriety". Descriptions of various clinical conditions are given, with detailed instructions as to indications for the use of many different foods and herbs. A practical approach to some of the problems of that day may be illustrated by the following quotation:

"Wine, Women, Bathes, by Art or Nature warm
Us'd or abus'd do men much good or harme."

The basic philosophy of Colonial medicine seems summed up in the following excerpts from the *Regimen Salerni:*

"Several kinds of Physicke may be good,
As diet, drinke, hot baths, whence sweat is growing,
With purging, vomiting and letting bloud.
The last of these is best, if skill and reason,
Respect age, strength, quantity and season."

Considering the probable hazards of surgical procedures employed at that time, the following instructions relative to bloodletting are of interest:

"Make your incision large and not too deepe,
That bloud have speedy issue with the fume
So that from sinewes you all hurt do keepe,
Nor may you (as I toucht before) presume
In sixe ensuing houres at all to sleep."

The implications as to the probable prevalance of subsequent hemorrhage are evident in the last line.

Among the more advanced theories of the following centuries concerning the cause and treatment of disease were those of Friedrich Hoffmann, who thought that a nervous fluid regulated motion, that excessive secretion caused spasm, and that a deficiency resulted in atony. For spasms, Hoffmann prescribed antispasmodics, sedatives and laxatives; and for atony, stimulants such as wine, camphor, quinine and ether. His prescribed therapy, as in all other systems, stressed venesection, diet, and mineral waters. Variations of these theories persisted up to the time of Benjamin Rush, who, in 1751, stated that medical therapy then in use consisted of "bloodletting, sweating, physicking, diuretics, vomiting and blisters".

Pioneers in American Medicine

There is a record of medicine practiced on this continent long before the arrival of settlers. In the year 1536, on the Gaspé Peninsula, Jacques Cartier, on the recommendation of the Indians, successfully treated an epidemic of scurvy among his crew by the use of a decoction made from the "Ameda" tree (probably a sassafras or spruce). This dread disease, which was said to have claimed, up to that time, some 10,000 seamen as victims, was not actually conquered until 250 years later. In 1753, Dr. James Lind's published investigations established the cure of this condition by lemon juice.

American physicians of English and Scotch descent and training took an active and important part in the early life of the colonies[3]. In Virginia, Dr. Walter Russell was one of the original Jamestown colonists. Dr. Lawrence Bohun was appointed Physician-General of Virginia in 1611, and Dr. John Pottes was temporary Governor in 1628. In Connecticut, Dr. John Winthrop, Jr. was Governor.

As for medical training, this was, for the majority of physicians, limited to the apprentice system, in which medical knowledge was obtained solely by working with a physician in his practice. In the 17th Century 134 practitioners were listed, including 12 surgeons[6]. The title of "doctor" was not used in the colonies prior to 1769. In 1776, there were 3,500 physicians, only 400 of whom had medical degrees[2].

Medical problems faced by physicians in America at that time were similar to those of the rest of the world, but were aggravated by lack of laws on sanitation and the shortage of drugs and equipment, as well as by the great distances that doctors had to travel to see their patients.

Because of the few trained doctors available, many ministers of the Gospel took up the practice of medicine. Although Smillie[6] describes our forefathers as "men of iron", the general health of the population was impaired because of unsanitary living conditions. In 1700, it was reported that smallpox had resulted in pock-marked faces of half the population of Europe. In Virginia, as reported by Bettman[2], the prevalent diseases in the 17th century were smallpox, plague, beri-beri, malaria and yellow fever. The prevailing diseases in New England were said to be typhoid fever, tuberculosis, pneumonia and scurvy. In 1610, 338 out of 398 colonists of Jamestown died; in 1621, half the population of Massachusetts perished. Infant mortality posed another problem, and in the 18th century there was in Europe an expected mortality of 75 per cent among newborn infants. Prior to James Lind's discovery, in 1753, of the preventive value of lemon juice, scurvy caused a mortality rate of up to 75 per cent among the crews of some ships. The life expectancy at this time was 35 years.

The high mortality rate was largely due to epidemics, which were usually introduced by ships' crews at seaports and which then swept through the colonies, decimating the colonists and, to an even greater extent, the Indians. The predominating epidemics of the 17th century were smallpox and measles; that of the 18th century, yellow fever[6]. The smallpox epidemics were finally controlled by inoculation of smallpox virus from active cases, notwithstanding violent opposition on the part of the public and some of the medical profession. In a smallpox epidemic in 1721, the Reverend Cotton Mather successfully, but secretly, inoculated his own son. In the same year Dr. Zabdiel Boylston also inoculated his son, for which he was mobbed. However, statistics repeatedly showed a death rate of about 15 per cent for natural smallpox and 2 per cent for those inoculated. This resulted in one of the major medical accomplishments of all time[6]. In a Boston epidemic of 1776, 9,152 persons were inoculated in 3 days, with total epidemic casualties of only 165 deaths. Following this remarkable result, General Washington ordered smallpox inoculations for the army, and widespread acceptance of the procedure followed. The mortality from inoculation was from one to two per cent in this country. The first successful cow-pox vaccination in this country was performed in 1800 by Dr. Benjamin Waterhouse of Boston, who used on his own son a dried vaccine obtained from Dr. Edward Jenner[6].

The pioneer frontier physician, as described by one of them, presents the following picture: "The doctor had to be his own pharmacist. He made his own pills and tinctures, compounded all his medicines, and generally carried all he required, as, with saddle bags across his horse, he wended his way from house to house. His life was one of peril, toil and privation. Every emergency, however grave, he was generally compelled to meet alone and unaided."

Because of the large number of untrained physicians and the prevalence of medical quackery, medical societies usually made an effort to supervise, control, and to license doctors. Certain state organizations fulfilled similar functions. As early as 1631, Nicholas Knapp of Boston was sentenced to be fined or whipped for "taking it upon himself to cure the scurvy, by a water of noe value, which he sold at a very deare rate"[6]. In 1636, the Assembly of Virginia decreed that the fees for surgeons and apothecaries should be 5 shillings, and for university-trained physicians, 10 shillings. Payments at that time, however, were apt to be in barter, consisting of wampum or tobacco, corn and other commodities. In 1649, medical licensure was established in Massachusetts, other states following in the course of time. In New York, an effort was made to regulate the practice of medicine by legislation in 1760, but it was not until 1797 that a state-wide law to license physicians after two years of study was passed.

In the early settlement days of Boston, medical practice was dominated by a single practitioner, Dr. William Douglass, described as "always positive and sometimes accurate", who was a graduate of the University of Edinburgh[4]. Later, during the Revolutionary period, the Warren brothers were predominant. Joseph Warren fell in battle at Bunker Hill. His dynamic brother, John, who was Director of the Hospital of the Continental Army in Boston, later gave the surgical lectures that led to the founding of the Harvard Medical School in 1782. Other early prominent medical schools were the Medical College of Philadelphia, which was founded in 1790, and that of Dartmouth College, founded in 1798. Among other centers of medical practice were New Haven and Sharon in Connecticut, and various cities in Maryland, Virginia and South Carolina.

In New York, Dr. Samuel Bard, also a graduate of Edinburgh, organized the medical school of King's College in 1767. As the "Professor of Physick", he was one of six professors initially appointed. He

was also instrumental in founding the New York Hospital, which was established in 1769 and incorporated in 1776. We are indebted to the "Stranger's Guide to the City of New York"[7], published in 1817, for a detailed description of that hospital. It was at that time made up of the hospital proper, which had 300 beds, the Lying-In Hospital (established in 1799), and the Lunatic Asylum (founded in 1808). On the staff were four visiting physicians and four visiting surgeons, "the most eminent in their field", as well as a resident physician and a resident surgeon. There was a library of 3,000 volumes. The hospital was "burnt by accident" in 1775 and reopened in 1791, at which time it admitted "infirm and friendless seamen". The New York Dispensary, "for the relief of the sick and poor", was incorporated by private subscription in 1795. Each subscriber paying five dollars a year was entitled to put two patients on the dispensary list during the year. The city was divided into six districts, with a physician assigned to each, "to give constant attention to the poor"[7].

Among physicians who attained eminence during the Revolutionary War were three Philadelphians, all graduates of the University of Edinburgh: John Morgan, William Shippen, and Benjamin Rush. Morgan was the original Director and Physician-in-Chief of the Continental Army and held this post until 1777, when he was succeeded by Shippen, who had organized the medical school of the University of Pennsylvania in 1765. Dr. Rush, who was an army officer, and took an active part in many civic affairs, founded the Philadelphia Dispensary in 1786. He was also Treasurer of the United States Mint (1799-1813) and a signer of the Declaration of Independence. Another Philadelphian, Benjamin Franklin, though not a physician, also made important contributions to medicine. Franklin's electrical experiments led to the trial use of shock therapy for paralysis; he invented bifocal lenses and a flexible catheter; he wrote and published many medical articles; and, in addition to all this, he was a founder and the first president of the Pennsylvania Hospital, in 1751. Altogether, this distinguished group of men gave Philadelphia a unique preeminence in American Medicine for having the first medical school, the first dispensary, the first humane society, the first general hospital, and the first philosophical society[4].

The accomplishments of the medical profession during the war were amazing, considering the conditions under which the doctors had to work[6]. The personal letters of Dr. John Cochran[8], appointed Director

of all military hospitals in 1781, give a grim picture of the most deplorable conditions imaginable. An apparently sincere, conscientious, sympathetic and able person, Dr. Cochran was constantly confronted with insoluble problems with regard to personnel, dissatisfaction, lack of discipline, resignations, and lack of money, supplies and equipment. Resignations were easily understandable in the light of Cochran's observations:

> "It is upwards of two years since many of us have received a shilling from the Continent, and there is as little prospect now of pay as there was two years ago."

Conditions concerning hospitals and patients were equally unsatisfactory, according to Cochran. In visiting the Albany Hospital, for example, he found a situation apparently similar to that in all other military hospitals, and reported as follows:

> "I found that hospital entirely destitute of all kinds of stores, except a little vinegar which was good for nothing; and frequently without bread or beef for many days."

Shortly after the Revolutionary War, physicians in all parts of the former colonies formed medical organizations for various purposes—to dispense charity, to supervise and license practitioners of medicine, to give one another assistance, and to aid in the dissemination of medical knowledge[2, 4]. As stated at that time by the New Haven Medical Society:

> "The late war brought many ingenious and learned physicians together from all parts of the continent, and formed them into a temporary society, whose unreserved communications have contributed to the improvement of medical knowledge and the establishment of a new and important era in the healing art."[4]

Between 1780 and 1790, a number of "Humane Societies" were formed in the larger cities, to treat suffocation caused by drowning and by other causes. Many medical societies were founded between 1779 and 1789, among which the better known were the Boston Medical Society, founded in 1780, and the College of Physicians of Philadelphia, founded in 1787. The general purpose of these societies was to regulate medicine, and to promote ethical practice and knowledge by publications. Dispensaries were founded in Philadelphia, in 1786, and in New York, in 1790.

Another important problem at that time was that of obtaining cadavers for dissection. Before authorization by law of the use of crim-

inals' bodies, resentment against the stealing of paupers' bodies by medical schools of New York resulted in the Doctors' Riots of 1788, in which mobs seriously threatened the lives of the doctors concerned. Grave-robbing also presented problems, as is shown by the personal account of a friend of mine, one of whose ancestors was a surgeon in upstate New York. Due to an error on the part of professional grave-robbers, a startled patient, on an evening emergency call to the doctor, found the body of one of the city's prominent citizens reposing in the doctor's surgery. The outcome was that the surgeon packed his family in the surrey that night and departed for the North, never to be heard of again in his home town.

American medical literature was practically non-existent prior to the Revolutionary War, and all reprints, periodicals and books were imported from Great Britain or the Continent. The first American medical book was published in 1769 and was written by Dr. Peter Middleton, who called his work *A Medical Discourse, or An Historical Enquiry into the Ancient and Present State of Medicine*. The only other American book noted by Garrison as existing in 1776 was one by a Dr. John Jones, entitled *Plain, Concise, Practical Remarks on the Treatment of Wounds and Fractures*. Otherwise, American contributions to medical literature at that time consisted of only a few tracts and reprints. However, following the war, a prolific literature soon resulted from the founding of medical societies, dispensaries and hospitals. Many articles printed in America were sent to Europe, where a considerable number were republished.

Methods in Early American Medicine

A personal insight into the practice of medicine in 18th century America has been furnished me by a ledger belonging to my son. This book, one of 47 on record, was carefully written by the pen of one of his Quaker ancestors, Dr. Wm. H. Stabler[9], who lived in Maryland. The entries date from 1799 to 1806, the year the doctor died. Among the charges listed are those covering drugs (mostly caster oil) and laxatives, such as salts, calomel, rhubarb and soda, and magnesia. Paregoric and laudanum were occasionally dispensed, as were "cooling powders for fever", itch ointment, and "blister plaisters". Other typical entries include "Dose of Salts for Billy .10", and "Carolina pink for black child .25". A purge was 15 cents, a "purge with vomiting .27". Surpris-

ingly enough, charges were also made for articles such as quarters of beef, veal, "old sheep", lambs, tobacco, corn, oats, drygoods and bricks.

The services rendered by Dr. Stabler and the charges for them are listed in the same manner. Visits were enumerated as "Visit to thyself 1.", "For visit and bleeding of thy wife 1.25", and "For visit to thy wife and lancing her breast 1.50". Almost all bills listed vaccinations, which were charged at $1.00. (Jenner's article on smallpox vaccination had appeared only in 1796.) It seems that one of the most common charges incurred was for bleeding, usually 25 or 50 cents. The charge for suturing an injured leg was $1.00; for one patient thus treated, laudanum and lead ointment were prescribed. The few bonesetting procedures listed are charged at $5.00 each. The cost of non-medical items is also of interest: A quarter of beef at 5 cents a pound came to $2.69, a quarter of veal at 6 cents a pound cost 78 cents. The "13 old sheep" netted $20.87, while the charge for "6 sheep at 1.00" was $9.00! At this point, we must at least suspect a Quaker trick to "outsmart thee".

The credit side of the ledger seems in general to balance with the charges, though in some instances, years elapsed between the date of the charge and the date of the payment. One entry indicated a payment made nine years after the death of the doctor, suggesting that at least in this case, the patient's "heart was in the right place". Non-cash credits included wool, beef, pork, veal and similar foods. A pig was worth $1.50; "285 pounds of pork delivered to Deborah Stabler" came to $20.64, a colt and a calf, $22.00, and a "service for mare 4.00". Two lots in Brookville were priced at $20.00; a quarter interest in a threshing machine at $20.69. Credit for labor covered services such as splitting rails, threshing, carrying chairs for the surveyor, and "For footing my boots, except for the uppers, 2.50".

An excellent insight into the theory and practice of colonial medicine worthy of some detail in discussion is afforded by the study of another book, published in Philadelphia in 1797, entitled *Domestic Medicine, or a Treatise on the Prevention and Cure of Diseases*[10], originally written by Dr. William Buchan of Edinburgh. The book was "adapted to the Climate and Diseases of America" by Isaac Cathrall. The front page is devoted to an "Advertisement" of the original author, in which he defends his right to publish a book, "to put people on guard in a dangerous situation, when the services of a physician could not be easily obtained". It is for this reason, it seems, that he had been "con-

demned by the medical faculty". The author furthermore complains that his book has been "mangled and mutilated" by counterfeit editions, which leads him to the conclusion that "laws protecting literary property are still in an imperfect state".

Without benefit of the bacteriologic knowledge of disease only available later, Dr. Buchan gives a good account of communicable diseases, their management and methods of transmission. He also treats physiology and hygiene in a most capable and modern manner. A discussion of the "Passions"—anger, fear, grief, love, and religious melancholy, reveals a considerable knowledge of psychosomatic disorders. Dr. Buchan states:

> "How the mind affects the body will in all probability, ever remain a secret. It is sufficient for us to know that there is an established reciprocal influence between the mental and corporeal parts, and that whatever injures the one, disorders the other. The best way to counteract the violence of any passions, is to keep the mind closely engaged in some useful pursuit."

Dr. Buchan makes accurate clinical observations on various conditions, such as fevers, with and without rashes, pleurisy, and pneumonia. He says:

> "What is called the crisis, or height of the fever, is sometimes attended by very alarming symptoms, as difficulty in breathing, irregular pulse, convulsive movements, etc. Bleeding is here improper."

Empyema is described thus:

> "Inflammation may lead to suppuration which is more or less dangerous. It sometimes breaks outwardly, and the matter is discharged in the wound. The matter may be discharged by expectoration. If the matter floats in the cavity of the breast, between the pleura and lungs, it can only be discharged by an incision between the ribs."

Diabetes Mellitus is considered a disease of the kidneys. The general treatment includes a hard bed and a "plaister to the back". The diet prescribed stresses mucilaginous foods and shell fish. Medications include "gentle purges" and astringents, such as equal parts of alum and terra japonica in a teacup of tincture of roses, taken three or four times daily. The diabetic patient is also described:

> "In a diabetes, the urine generally exceeds in quantity all the liquid foods. It is thin and pale, of a sweetish taste, and an agreeable smell. The patient has a constant thirst, with some degree of fever, his mouth is dry and he spits frequently a frothy spittle. The strength fails, the appetite decays, the flesh wastes away until the patient is reduced to skin and bones. Frequently the loins, testicles and feet are swelled."

Comments by Dr. Buchan on the significance and causes of hemorrhage are of interest:

> "Spitting of blood is not always a primary disease. It is unfavorable in pleurisies, peripneumonies, and sundry other fevers. In dropsy, scurvy, or consumption it is a bad symptom, and shows that the lungs are ulcerated."
>
> "Vomiting of blood may occur as the result of hysteria, plethora, obstruction of the menses in women, stopping the hemorrhoidal flux in men, anything that stimulates or wounds the stomach, or such conditions as obstruction of the liver, malignancy, or tuberculosis."

Blood in the urine is described as due to:

> "Injuries from carrying heavy burdens, hard riding, stones or malignant diseases. This is always dangerous, especially when the blood is mixed with purulent material."

The treatment prescribed is bleeding for plethora, operation for stone, bark and acids for malignancy. Hemorrhage of the bowel, known as "bloody flux", is ascribed to:

> "obstruction of the perspiration, dysentery and infectious communicable disease, in which case even the smell of the patients' excrements have been known to communicate it."

In contrast to the remarkably good hygienic practices and the excellent clinical observations described in the treatise, diagnostic and laboratory procedures were apparently most inadequate, as was the rationale of many of the therapeutic procedures prescribed. For example, there was apparently little concern about accurate physical findings in those days, and there is hardly any mention by Dr. Buchan of percussion, auscultation or laboratory procedures.

It is in the field of internal disorders (not susceptible to direct observation) where most of the misunderstandings and fallacious treatment seem to occur in Dr. Buchan's book. Under the title, "Inflammation of the Stomach", a clinical description is given suggestive of peptic ulcer, including hemorrhage and obstruction. This condition, Dr. Buchan states:

> "May end in a suppuration, and sometimes in a mortification (as shown by tarry stools) which is certain death. When the patient vomits everything he eats or drinks and is extremely restless, has a hiccup, or an intermitting pulse, or frequent fainting fits, the danger is very great."

The treatment prescribed for peptic ulcer is bleeding, "repeated as long as the pulse rises"; afterward, hot abdominal applications, "plaisters to the abdomen, and hot bricks to the feet". The diet prescribed is bland, except in cases of vomiting, in which nothing is given by mouth and

nourishment is provided by nutritive "clysters" (enemas).

Under "Inflammation of the Intestines", there are descriptions of clinical conditions suggesting acute appendicitis and intestinal perforation or obstruction, classified as "Iliac Passion" and "Enteritis". Abdominal pain and vomiting are described as the predominating symptoms, as follows:

> "Sometimes even the excrements, together with the clysters and suppositories, are discharged by the mouth. Clammy sweats, black foetid stools, with a small intermitting pulse, and a total cessation of pain, are signs of mortification already begun, and of impending death."

The treatment prescribed for apparent appendicitis is similar to that of inflammation of the stomach, except that if hot applications are not effective in the relief of symptoms, strong purges are advised. Laudanum and acids are recommended, and for the most critical cases there should be given "hot baths, walking on a wet pavement, or quicksilver by mouth", "a few ounces to the pound". It is admitted that:

> "Indeed these (treatments) are attended with some danger, but a doubtful remedy is better than none."

Operation was advised only for external ruptures, which could not be relieved by hot applications or "gentle pressure with the hand". Otherwise, surgery seemed largely limited to conditions such as lithiasis, tracheotomy and empyema.

Dr. Buchan's only observations on laboratory examinations coming to my attention are included in a footnote on "urine doctors".

> "The appearance of urine is very uncertain, and very little to be depended upon. Anyone who attends to this will be astonished at the impudence of those daring quacks, who pretend to find out disease, and prescribe to patients from the bare inspection of their urine. Many of them amass considerable fortunes. The common people still have an unlimited faith in their skill, although it has been demonstrated that no one of them is able to distinguish the urine of a horse from that of a man."

In conclusion, notwithstanding the lack of laboratory tests and the inadequacy of knowledge concerning internal disorders and surgical procedures, the practice of medicine during the 17th and 18th centuries received a tremendous impetus in its evolution from the empirical therapy of previous centuries to the scientific approach to medicine as practised today. This progress was made possible by the scientific and cultural developments of the period, as well as the establishment in Great Britain and on the Continent of great universities, medical schools,

hospitals, dispensaries, medical societies, and medical publications. American men of medicine who, before the Revolutionary War, were trained almost entirely in Europe or by the apprentice system in the colonies, made contributions to medical practice after the war that were far greater in importance than could have been expected from them, considering the adverse conditions under which they worked.

Many medical contributions at that time were the basis of procedures that have only recently been widely publicized as developments of "modern" medicine. For example, it is well to remind ourselves that mouth-to-mouth resuscitation was successfully practiced in 1743 on a miner by Dr. William Tossach, of England; that Benjamin Franklin advocated shock therapy for paralysis in 1753; and that in 1779, hypnotism was practised by Mesmer, in France. (The Marquise de Lafayette thereafter made efforts to introduce hypnotism into the United States, only to be repulsed by a skeptical medical profession.) Finally, on the subject of our highly advertised tranquilizers, we find that one, at least, was apparently in common use for centuries before 1607, as indicated by the following passage from the *Sanitatis Salerni:*

> "Ellecompane strengthens each inward part,
> A little looseness is thereby provoken,
> It swageth griefe of minde, it cheeres the heart,
> Allaieth wrath, and makes a man faire spoken."

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NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

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Vascular Alterations in Connective Tissue Disease

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Many facets of the problem of arteritis in relation to hypersensitivity are highly controversial and since I have made no specific studies in this connection, this presentation will be largely based upon an evaluation of the literature and personal experience.

Periarteritis nodosa was first recognized about 90 years ago. The medium-sized muscular arteries were involved, with a predisposition for the splanchnic area. Few lesions of terminal arterioles or veins were noted and the pulmonary vessels escaped.

After 1925, the concept that the disease was a hypersensitive reaction to a non-toxic agent grew, and seems now to be almost universally accepted, although the offending antigen in many cases remains obscure.

Friedberg and Gross[1] (1934) described four cases of periarteritis nodosa in which there was typical rheumatic carditis as evidenced by Aschoff bodies. It is easy to be wise in retrospect, but can we not now explain the findings in these cases on the basis of rheumatic fever alone? Gross considered several other cases of polyarteritis to have an associated rheumatic fever, but these were not included because they did not fulfill his rigid criteria for a diagnosis of rheumatic fever. He expressed the opinion that the association of these two conditions was more frequent than was generally recognized.

A most significant advance was that of Rich[2], with the observation of polyarteritis in five patients dying of serum sickness, four of whom had received sulfa drugs so that it was necessary to consider the factor of drug sensitivity. His report stimulated much experimental work, on the basis of which hypersensitivity has been established as the principal factor in the production of necrotizing arteritis, presumably the result of an antigen-antibody combination at some site within, or adjacent to, the vascular wall.

The case for hypersensitivity as a causative factor is supported by the observation that bronchial asthma is frequently complicated by vascular alterations such as one observes in polyarteritis[3]. Looking at the problem in reverse, of 300 cases of polyarteritis, 54 (or 18 per cent) had asthma (described as allergic granulomatosis). Wegener's granulomatosis is another condition in which there is a destructive lesion of the respiratory tract, arteritis and nephritis.

The labelling of such entities as granulomatous may be helpful from a clinical standpoint, yet I fail to see much advantage because the basic pathologic alteration of these two conditions (allergic and Wegener's granulomatosis) is primarily a vascular one. The wide variability of response in different cases would seem to signify quantitative differences modified by such

factors as the duration of illness, nature of the antibody response, the antigen-antibody ratio and the level of sensitization of the host. Most workers find it advantageous to designate cases associated with allergy as hypersensitivity arteritis or angitis, and to separate them from classical polyarteritis, the principal difference being that in the former condition (hypersensitivity arteritis) the small vessels—arteries, veins, as well as capillaries—are involved, and the pulmonary vessels are not exempt. I have never analyzed our cases to check this point, but am of the opinion that when tissues are widely examined in all cases, there are frequent exceptions to this pattern.

Although great emphasis has been placed on hypersensitivity in the pathogenesis of arteritis, other significant factors may operate in the various forms of vascular disease under discussion. Such factors as hypertension, the administration of certain steroids, or large amounts of sodium, might each appropriately be discussed at length. I will mention only one point in this connection. A recent observation by Campbell and Santos-Buch[4] indicates that in the rabbit there are differences between the vascular lesions incited by sensitization with horse serum when contrasted with those produced by constricting one kidney with silk, followed by contralateral nephrectomy. In these experiments the vascular alterations preceded the development of hypertension and did not correlate with it.

Of interest in the light of current therapy are the findings in the vascular system of patients with rheumatoid arthritis, a disease not usually associated with hypersensitivity, but for which one can make a strong case. A recent report[5] has attributed three deaths to vascular lesions associated with gangrene of the extremities in patients receiving steroid therapy. The histologic findings presented are indistinguishable from those observed in polyarteritis. For the five year period, 1953 to 1957 inclusive, the deaths of 36 patients with rheumatoid arthritis and arteritis attributed to steroid therapy have been reported.

Before incriminating therapy, the status of the blood vessels prior to the use of steroids must be considered. It is known that a variety of vascular lesions may occur in the synovial membrane, coronary arteries or skeletal muscles of patients with rheumatoid arthritis.

Sokoloff, Wilens and Bunim[6] (1951) described arteritis in the striated muscles of five of 57 cases of rheumatoid arthritis who had never received steroids. They pointed out that rheumatoid arteritis is unlike periarteritis in several significant respects. In 1957, a report[7] on ten cases noted the increasing frequency of the condition and the possibility that some of the alterations resulted from the deleterious effect of steroid therapy. They emphasized the wide spectrum of lesions and now noted some of their cases to be indistinguishable from periarteritis nodosa.

Bywaters[8] has described peripheral vascular disease in the extremities of seven patients with rheumatoid arthritis who had never received steroids. If steroid therapy does aggravate the vascular lesions, and the evidence suggests that it does, there is need for greater precaution in treatment, even though steroids have a known beneficial effect upon polyarteritis.

(The findings in three cases were presented to illustrate the points discussed. These included the autopsy findings on a patient with rheumatoid arthritis and extensive vascular alterations, and a fatal case of thrombotic thrombocytopenic purpura attributable to formalin sensitivity; also a patient with a history of rheumatic fever, tuberculosis, and drug sensitivity whose biopsy revealed necrotizing vascular alterations.)

I would like to diverge for a bit and report upon a recent observation by Dr. Hartmann[9] of our department. During a study on carcinogenicity of various fluorinated derivatives of 10 methyl 1,2 benzanthracene (10-Me-BA), all rats injected subcutaneously with the 4'-fluoro derivative died within eight weeks. Conspicuous alterations were observed in the vessels of the lungs and kidneys of these animals.

The lesions were first observed in the lungs of a rat killed two weeks after injection of 4'-fluoro-10-Me-Ba. By the fourth week four of seven animals had advanced lesions in the pulmonary and/or renal ves-

sels, and all but one killed thereafter had lesions. The larger branches of the pulmonary and bronchial arteries are involved. The media is edematous and infiltrated with polymorphonuclear leukocytes and fibroblasts. Necrosis usually involves segments of the vessel walls. In the kidneys the conspicuous alteration is hyaline necrosis of the afferent arterioles, which occasionally involves a portion of or the entire glomerulus. Lesions are reminiscent of those seen in malignant hypertension.

The renal lesions were most pronounced at four and five weeks, but absent after seven and eight weeks. This suggests that the lesion is reversible. Hawn and Janeway[10] observed regression of vascular lesions induced in rabbits by the administration of foreign proteins; such regression was correlated with a decreased level of circulating antigen.

The lack of such lesions in rats given the parent hydrocarbon 10-Me-BA or the 3-fluoro derivative would tend to exclude a toxic effect, as would the delay in development. Such a delay in development strongly suggests that chemical sensitivity is the principal etiologic factor. Sensitization to 9,10 dimethyl-1,2-benzanthracene has been reported following topical application in a human volunteer.

Various polycyclic aromatic hydrocarbons have been shown to combine with certain tissue proteins of the mouse *in vivo*. Should the 4'-fluoro-10-Me-benzanthracene compound likewise combine with one or more proteins *in vivo* and yield an antigenic foreign protein, auto-immunization would result. I have cited this experiment for two reasons: 1) Such an experiment may give us another entering wedge with which to explore the pathogenesis of arteritis under controlled experimental conditions. 2) It should also alert us as pathologists to the possibility of an increasing development of arteritis in patients currently receiving a battery of chemotherapeutic as well as other chemical agents.

From the foregoing it is evident that the vascular lesions in a wide variety of conditions result from a reaction of antigen and antibody, and although the basic mechanism may be similar, different degrees of reactivity result in a wide variety of tissue alterations. Some are acute and fulminating, with or without eosinophilia; some have an intense plasma cell reaction indicative of antibody response. Others resemble granulomata with giant cell reaction. Ultimately, as the process subsides, reparative fibrosis predominates.

I do not wish to minimize microscopic morphology, yet it seems that perhaps we are focussing too intently upon this phase of the problem. If forced to place the above conditions into separate categories on the basis of microscopy alone, most of us might fare rather badly. This indicates that there are few, if any, specific anatomic characteristics by which such lesions can be accurately separated. In other words, there are sufficient similarities to suggest that the alterations in each condition, although due to different etiologies, are produced by somewhat similar mechanisms.

Let us look at vascular disease in general and then at arteritis in particular. There seems to be little question that arteriosclerosis is a man-made disease, that is, if one accepts the fact that diet, stress and genetics are significant. In the case of arteritis we apparently have another such disease. Since the time of Jenner, foreign proteins have been injected into man. During the early days of immunization large amounts of horse serum were administered.

High-priced stocks of pharmaceutical houses are a reflection of the amount of chemicals being administered as drugs, many of which are capable of combining with proteins to act as potential sensitizing antigens in susceptible individuals. Although the present danger from such toxicants is considerable, it may be much greater for subsequent generations.

What are the responsibilities of the pathologist in this problem? Since we alone make the definitive diagnosis, we have some contact with all cases of arteritis and therefore have an unusual opportunity to follow the course with repeat biopsies and at necropsy. We also uncover the nonsuspected case in surgical specimens or from the postmortem examination, as in cases that I have cited. Because of our unique relationship with all medical services, we

are probably most familiar with the increasing incidence of this group of diseases and should so inform the profession.

I should also like to make a plea for more extensive investigative interest in this area by pathologists, utilizing the newer tools at hand. Fluorescent antibody and isotope techniques seem to offer certain opportunities. This is a problem that will require a broad knowledge of immunology, biochemistry and genetics for its solution, yet it would seem that ultimately an insight into tissue structure and cytology will also be of paramount interest. Of all scientists, the pathologist seems admirably equipped to solve the problem. The greatest need, however, is for bright young men with energy, enthusiasm and imagination.

*Experimental Coronary Thrombosis and Myocardial Infarction Induced by Diet in Rats**

WILBUR A. THOMAS

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We have previously reported a dietary method for the production of arterial thrombi and infarcts in rats involving the feeding of semi-synthetic diets that included large amounts of fat, cholesterol, propylthiouracil and bile salts as basic ingredients[11, 12]. One of the diets (containing 40 per cent butter) used in the original experiments has been repeated in six subsequent experiments with an over-all incidence of infarcts varying from 7 per cent to 60 per cent (average 20 per cent). However, when only those rats that survive for two months are considered, the incidence of infarction is much more constant (average 27 per cent). In addition, 38 modifications of the above diet have been fed to separate groups of rats. Many of these have resulted in a similar incidence of infarcts; others in a lower incidence or absence of infarcts; none in a clearly higher incidence. In substitution experiments, diets containing either butter, lard or Crisco (along with other basic ingredients) have had a similar high incidence, but diets containing large amounts of corn oil (otherwise plus the same basic ingredients) have produced practically no infarcts. In omission experiments, no single ingredient has been found to be absolutely essential for the production of infarcts, but the absence of any of the basic ingredients has resulted in a drastically lowered incidence.

Cholesterol levels in the blood rise rapidly in rats on all of the infarct-producing diets, but levels have not been significantly higher in those with infarcts than in those without. Further chemical studies are planned.

A method has been developed for the study of clot-lysis in rats on infarct-producing diets utilizing the thromboelastograph. Under the conditions of the experiment it has been demonstrated that clots from rats on certain of the infarct-producing diets (containing butter) lyse more slowly than those from rats on similar diets in which corn oil is substituted for butter. Experiments with the thromboelastograph are being expanded in work now in progress with Drs. R. F. Scott and A. S. Daoud in an effort to identify the specific hematologic alteration and the specific chemical factor that causes the alteration.

It is our belief that arterial thrombosis in man and animals results from the interplay of two factors: 1) a local factor, usual-

* The experiments reviewed herein were done in collaboration with Drs. W. S. Hartroft and R. M. O'Neal of Washington University in St. Louis and with the aid of PHS grants H-1820 and H-4727.

ly atherosclerosis, and 2) a hematologic factor, either procoagulative or antifibrinolytic or both. In the experiments reported herein we believe that the principal effect has been on the hematologic factor.

DISCUSSION

SIGMUND L. WILENS: I want to start by saying that I admired Dr. Angevine's scholarly and logical presentation of the various types of non-infectious, allergic arteritis, and I find I can hardly take exception to any of the major opinions that he expressed. This will not make for a lively discussion, since I do not have any objections to what he said, but I might elaborate just a little bit on the arterial lesions he described in association with rheumatoid arthritis. Dr. Sokoloff[13], at the time he was studying the focal lymphocytic accumulations in muscle, which were considered to be specific for rheumatoid arthritis, made a rather extensive study in which he cut muscle biopsies in serial section and stained every fifth section, so that we ended up with 300 or 400 slides from each block, and of these we found only one or two had any arterial lesions at all. It is obvious, therefore, that at least in the pre-steroid era, it was like looking for a needle in a hay-stack to find these lesions. They did not have the severity of the lesions Dr. Angevine found. His lesions outshadowed ours by far. Many of us have seen the bizarre type of case of rheumatoid arthritis which, while under heavy steroid therapy, suddenly develops systemic disease with marked arterial involvement and granulomatous lesions of the spleen and other organs, producing a picture which is not unlike Wegener's granulomatosis without the kidney lesions. I have no explanation for it other than to suggest that some new type of hypersensitivity comes into play, and I have no further comment to make.

Regarding Dr. Angevine's statement that all of these vascular processes belong in the same group, and that we are probably not justified in attempting to segregate them too sharply, in general, I agree with that too. I think, however, there are patterns of lesions that fall into fairly distinct groups. Dr. Angevine mentioned the work recently reported from Cornell[4, 14] in which the arterial lesions produced in rabbits by massive injections of horse serum differed from those of experimental hypertension. When I was an interne in pathology I was working under Drs. Pappenheimer and von Glahn, who were studying arteritic lesions that they found in certain cases of active rheumatic fever. They felt that this lesion was different from the lesion of periarteritis nodosa, although I think they were hard put to it to describe what the difference was. They believed, however, that in rheumatic arteritis, no matter how severe the inflammatory process in the arterial wall might be, the lumen almost never became thrombosed. In other words, they felt it was not the endothelium of the vessels that was attacked, but it was the extracellular substances of the vessel wall. In periarteritis nodosa, however, thrombosis is a common complication. It is interesting that in the inflammatory lesions produced by Rich[15], and since then by a host of others, by intravenous injection of massive amounts of horse serum into rabbits, the intense inflammatory lesions which develop, in coronary arteries particularly, also do not become thrombosed. This, to my mind, puts them a little more in the category of the lesions of rheumatic disease rather than periarteritis nodosa. I feel it is justified to separate these two.

As I say, I enjoyed Dr. Angevine's presentation. After all, he is a pathologist of my own vintage; he speaks the same language that I do. The coinage of new words that have come into the pathological vocabulary in recent years is sometimes quite distressing, and it is gratifying that Dr. Thomas did not use the word "infarctoid" in his presentation. I was rather afraid that he might, not that he is responsible for coining that word. In any case, I think the presentation of Dr. Thomas, if I may turn to that now, is more exciting because it is newer, and I think it is more controversial.

About 50 years ago, when the first successful experimental production of dietary arteriosclerosis was reported[16], the average pathologist was not willing to accept it at all. He was so deeply imbued with the idea

that arteriosclerosis was a degenerative disease that he could not accept the concept that it could be produced by feeding animals special diets. The pathologists at that time interposed many objections to the idea that this experimental lesion was at all comparable to human arteriosclerosis. I think through the years we have seen some of these objections answered. Originally this dietary lesion was thought to be a peculiarity of the rabbit. Later, Forest Kendall[17], taking advantage of the fact that thiouracil would slow down metabolism, was able to produce the same lesion in dogs by combining cholesterol feeding with thiouracil. More recently, Rosenman, Byers and Freedman[18] reported that the feeding of cholesterol and bile salts to rats at the same time would cause a fairly decent elevation of blood cholesterol to about 200 to 250 mg. per cent. Shortly thereafter, Fillios and the Boston group under Dr. Stare decided to combine all three procedures[19]. Rats under this triple regimen did develop severe hypercholesterolemia and eventually atherosclerosis, and in a very few instances, I believe, they developed myocardial infarcts. I do not know how comparable those few infarcts are to yours, Dr. Thomas. Also Dr. Deming[20], working at Goldwater Memorial Hospital, has used the triple threat, if you will permit me to call it that, plus making his animals hypersensitive by putting a clip on one renal artery, and when he does this, he increases the severity of the atherosclerotic lesion in the rats. After three or four months he found a fair percentage of myocardial infarcts, though he tells me this varies with the strain of the rats used. In some instances the incidence was comparable to some reported by you, Dr. Thomas. For example, in one experiment, five in a group of 30 developed infarcts. In the Deming experiment, the cardiac lesions were more conventional, in the sense that they were associated with occlusive atherosclerotic lesions in the coronary arteries, which I gather Dr. Thomas did not find.

Dr. Thomas's findings introduce a brand-new concept in the pathogenesis of myocardial infarcts. The arteriosclerotic lesion itself, although it might be an inciting factor, would not appear to be a necessary precursor to myocardial infarction, according to your findings. I think it should also be pointed out that when we feed cholesterol to a rabbit, we do get lipid deposits in the coronary arteries, but the appearance of the arteries is strikingly different from the appearance of the coronary artery in human atherosclerosis, and myocardial infarcts do not develop. I do not think anyone would deny that. The lipid does not stay in the intima of the coronary artery of the rabbit. We find it permeating through the media and causing increased thickening of the vessel wall, but this increased thickness affects only the external diameter. The vessel becomes thicker on the outside, but the lumen remains the same in size, whereas in human atherosclerosis the lipid deposits are confined to the intima. It is true that in the experimental atherosclerotic lesion the lipid does penetrate more deeply into the media than is usually seen in human spontaneous atherosclerosis, but this may be related to the intensity of the process and the tremendous elevation of blood cholesterol, which is associated with these lesions. This is in sharp contrast to what is usually seen in man. In any case, the production of infarcts in this one species, the rat, I think, has removed another major obstacle to accepting the idea that myocardial infarction may be related to dietary habits, such as the consumption of large amounts of cholesterol and other materials.

In preparing for this discussion I read Dr. Thomas's original paper[12] which appeared about two years ago, and also a manuscript of a paper now in press, which he was good enough to send me. On reading these, a number of questions occurred to me about the nature of the infarction and of the vascular lesion which I hoped he might answer in his presentation tonight, but Dr. Thomas has probably repeated this material so many times that he was more interested in talking about his more recent studies. I have prepared a number of questions concerning the nature of these vascular lesions and cardiac lesions which I think might help me, at least, and possibly other pathologists, who try to interpret the significance of Dr. Thomas's results in terms

of human infarction. You may say you are not primarily interested in that at the moment and yet a comparison of the two lesions is inevitable. I do not think it would be cricket, however, for me to ask questions about data which Dr. Thomas did not present here, do you, Dr. Zimmerman?

H. M. ZIMMERMAN: No, I do not think it would be cricket.

SIGMUND L. WILENS: I agree it would not be fair to ask questions on material not presented here, so I shall not do so.

QUENTIN BURRITT DEMING: I would like to ask Dr. Thomas two questions. The first is, what do the rats who die in the first few months die of? What sort of state are these animals in? The second question is relevant to the fascinating data you were presenting on the technique for measuring the lysis of the clot. You presented the cholesterol levels by groups. They were at extraordinary heights, and the group with the highest cholesterol had the longest clot lysis time. I wonder whether you know what the correlation was between the lysis time and the cholesterol level. What I am getting at is this: is it conceivable that this technique is merely measuring something directly related to plasma lipid?

WILBUR A. THOMAS: It is even harder to say in these rats what they die of than it is in man; I do not know what the rats die of at any time in these experiments, with the exception of about 10 per cent who died of infection. The rats for the most part are immature, weighing 100 grams (at maturity on a normal diet they should weigh 400 grams) and with thiouracil alone they will stop growing. The weight stays about the same throughout the experiments. The rats do not look well; they are not in good condition; they are at the verge of the absolute limit they will tolerate, because whenever we tried to raise the incidence of the lesions by increasing any factor in the diet, all the rats would die in a short time, so we knew we were giving them a "bad" diet. For the most part we could not tell what the rats died of; they die without anatomic lesions to explain the death, except that they had fatty livers, and so on. One very curious thing, or perhaps not curious, but one of the facts, was that the rats with infarcts lived just as long as the rats without infarcts. When we averaged the duration of life after the beginning of each experiment, we found that those who had infarcts lived as long as those who did not have infarcts. Many of the infarcts were large enough so that they might have caused death, or at least we would have expected them to in man.

In regard to your other question, we have no information on which to base an answer. What I presented were the only positive results we have gotten so far. The blood cholesterol levels in the rats in our experiments on infarct-producing diets were around the 2000 mg. per cent range, whether or not the rats had infarcts. All we were measuring was cholesterol, but obviously many other lipid elements were increased; at the time, cholesterol was all we knew how to measure in our tissue laboratory. The plasma looked like melted butter in many of these animals. As to which one of the elements in the diet or blood produces the effect on lysis we do not know. Our next step is to try to find out the specific chemical factor or factors that are involved.

RICHARD M. TORACK: Have you tested the blood of ulcer patients who are on Sippy diets to determine if there is prolonged lysis of clots?

WILBUR A. THOMAS: No, we have not. We would like to, and we would also like to test the blood of Uganda natives, who have virtually no infarcts, against our Albany citizens, who appear to have the highest incidence of infarcts in any part of the country, but we have not done anything about it as yet. One thing Dr. Wilens said I would like to comment on. Perhaps I expressed myself poorly, but I did not intend to imply that I am not interested in man. What I wanted to say is that I do not feel we are warranted as yet in drawing conclusions in regard to man from these experiments. However, we are working with rats because we are interested in man.

HENRY G. SCHMIDT, JR.: I would like to know if any of your vascular occlusions were related to intrinsic disease of the blood vessel walls. Did you have occlusions related to vascular lesions?

WILBUR A. THOMAS: No thrombotic occlusions could be related to specific local vascular lesions. Some fat was present in all coats of arteries everywhere, but no real plaque formation. We did serial sections of these hearts, and before I left St. Louis, as a matter of interest, I counted how many sections had been cut, and it was something over 20,000 sections. We used the carbowax technique, which makes it possible to do fat stains on anything you want in serial sections, and we did four different stains. I saw no connection with any local lesion in the vessel wall with thrombosis in any single animal. I saw fat in vessel walls, and saw fat in the thrombi, wherever they occurred, but I did not see any more fat in the vessel walls at the site of thrombosis than elsewhere, nor in thrombi than in ordinary postmortem clots in these rats. We looked at tissues with the light microscope, the phase microscope, and the electron microscope, and have seen no local lesion in the vessel walls that explains the thrombus in any terms that we understand in man. I think we are mainly doing something to the clotting systems in these animals. Fat is present in the arterial walls and it is possible that the fat in the vessel wall has *something* to do with the thrombosis, but I am convinced that the main effect is on the blood itself in these animals.

GEORGE E. MURPHY: Do fat stains of the heart reveal any fatty alteration in heart muscle cells in the rats in your experiments?

WILBUR A. THOMAS: In the infarcts we saw fat, of course, and the more fat the animal got, the more fat we saw in the infarcts. In the muscle away from the infarct we did not see fatty change. I might make one comment here about "infarctoid", since Dr. Wilens used that term. We called the lesions in our rats infarcts because we think they are infarcts; they look like infarcts, and not like foci of necrosis from other causes. I have done experiments in which we injected streptokinase and also infected animals with hemolytic streptococci and produced multiple areas of necrosis in the myocardium; also we gave massive doses of vitamin D and produced multiple areas of necrosis in the myocardium, but mostly small, focal lesions, "metabolic lesions", if you will. I do not think that we are producing "metabolic lesions" in the animals described tonight. We usually found only single lesions having the configuration of infarcts; we did not find multiple areas of necrosis or degeneration or anything else. The muscle in the areas, except for the infarct, looked all right.

JAMES I. BERKMAN: May I ask Dr. Angevine one question? Regarding the rats with arterial necrosis, were these animals hypertensive?

D. MURRAY ANGEVINE: No measurements of blood pressure were made on these animals. On the basis of the histology of the vasculature in the kidney one might expect that there was some degree of hypertension. In view of the probable reversibility of these lesions it would be of considerable interest to investigate them further from the standpoint of altered renal physiology.

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THE NEW YORK ACADEMY OF MEDICINE

FOURTH ANNUAL POSTGRADUATE WEEK

OCTOBER 24 to 28, 1960

FRONTIERS IN MEDICINE AND SURGERY — 1960

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All physicians, including interns and residents, and those working in the allied sciences, are cordially invited to attend all sessions

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SCIENTIFIC EXHIBIT

The Scientific Exhibit will open officially at 11 a.m. WEDNESDAY, OCTOBER 19, 1960 and be open daily 10 a.m. to 10 p.m. through October 28, except Saturday and Sunday, October 22 and 23.

All inquiries should be addressed to:

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FOURTH ANNUAL POSTGRADUATE WEEK

OCTOBER 24 to 28, 1960

FRONTIERS IN MEDICINE AND SURGERY — 1960

PANEL MEETING — 4:30 P.M.

Monday October 24

RECOGNITION AND MANAGEMENT OF COMMON VIRAL DISEASES

Moderator: YALE KNEELAND, JR., M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M.

GENETICS

G. W. BEADLE, Ph.D., *California Institute of Technology*

GENETICAL VARIATIONS IN THE SERUM PROTEINS OF MAN

ALEXANDER G. BEARN, M.D., *The Rockefeller Institute*

PANEL MEETING — 4:30 P.M.

Tuesday October 25

ARTERIAL OBSTRUCTION IN THE EXTREMITIES: MEDICAL AND SURGICAL ASPECTS

Moderator: JERE W. LORD, JR., M.D., *New York University Post-Graduate Medical School*

LECTURES — 8 P.M.

CLINICAL IMPLICATIONS OF CYANOSIS

HARRY W. FRITTS, JR., M.D., *New York University College of Medicine*

PRESENT UNDERSTANDING OF THE ROLE OF GLIADIN IN THE STEATORRHEA SYNDROMES

CHARLES D. MAY, M.D., *College of Physicians and Surgeons, Columbia University*

PANEL MEETING — 4:30 P.M.

Wednesday October 26

"AUTO-ANTIBODIES" AND DISEASE

Moderator: HENRY G. KUNKEL, M.D., *The Rockefeller Institute*

LECTURES — 8 P.M.

CURRENT STATUS OF BONE MARROW TRANSPLANTATION

J. W. FERREBEE, M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M. (continued)

Wednesday October 26 *(continued)*

CURRENT STATUS OF BONE TRANSPLANTATION
CAPTAIN G. W. HYATT, MC, USN, *U. S. Naval Medical College*

CURRENT STATUS OF KIDNEY TRANSPLANTATION
JOSEPH E. MURRAY, M.D., *Harvard Medical School*

PANEL MEETING — 4:30 P.M.

Thursday October 27

THE VALUE OF ANTIBACTERIAL PROPHYLAXIS IN MEDICAL AND SURGICAL PROCEDURES
Moderator: WALSH McDERMOTT, M.D., *Cornell University Medical College*

LECTURES — 8 P.M.

MUSCULAR DISEASE
DAVID GROB, M.D., *State University of New York, Downstate Medical Center*

PYELONEPHRITIS
EDWARD A. GALL, M.D., *University of Cincinnati College of Medicine*

PANEL MEETING — 4:30 P.M.

Friday October 28

RECOGNITION AND MANAGEMENT OF THE COMMON PSYCHONEUROSES
Moderator: DANA W. ATCHLEY, M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M.

NUTRITION AND THE BRAIN
RAYMOND D. ADAMS, M.D., *Harvard Medical School*

SURGICAL ASPECTS OF INTERNAL CAROTID OBSTRUCTION
MICHAEL E. DeBAKEY, M.D., *Baylor University College of Medicine*

NEUROLOGICAL ASPECTS OF INTERNAL CAROTID OBSTRUCTION
H. HOUSTON MERRITT, M.D., *College of Physicians and Surgeons, Columbia University*

BUFFET SUPPER

A buffet supper will be served each evening in the Presidents' Gallery at $3.75 per person. It is felt this will add to the pleasure of the interlude between the afternoon and evening sessions. *Advance Reservation and Check* (payable to The New York Academy of Medicine) must be received no later than Monday, October 17, 1960.

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The Glorney Foundation has provided a grant in support of this initial course, accordingly **NO FEE** will be charged.

OBJECTIVES OF THE COURSE

The purpose of this course is to provide a basic review of selected aspects of the several human organ systems, with particular emphasis on their physiology, pharmacology and biochemistry as related to clinical disease. The course will consist of a series of seminars with active audience participation.

* * * * *

METABOLISM AND FLUID AND ELECTROLYTES

September 6, 1960

ORAL NUTRITION
Herbert Pollack

PARENTERAL NUTRITION
Theodore B. Van Itallie

September 13, 1960

INTERMEDIARY METABOLISM
Maurice E. Shils

METABOLISM AND FLUID AND ELECTROLYTES (continued)

September 20, 1960

DIFFERENTIAL DIAGNOSIS OF ELECTROLYTE ABNORMALITIES
Parker Vanamee

PRACTICAL CORRECTION OF ELECTROLYTE ABNORMALITIES
J. William Poppell

September 27, 1960

DIABETIC ACIDOSIS AND RENAL ACIDOSIS
Albert L. Rubin

RESPIRATORY ACIDOSIS AND ALKALOSIS
J. Frederick Eagle, Jr.

CARDIOVASCULAR SYSTEM

October 4, 1960

HEMODYNAMICS OF CONGESTIVE HEART FAILURE
Saul J. Farber, Ludwig W. Eichna

October 11, 1960

CARDIAC ARRHYTHMIAS
Chandler Mc. Brooks, Herbert J. Kayden

October 18, 1960

HYPERTENSION
George A. Perera, Quentin B. Deming

November 1, 1960

DISORDERS OF THE CORONARY ARTERIAL SYSTEM
Howard A. Eder, William Dock

November 7, 1960

THROMBOSIS AND EMBOLISM
Irving S. Wright

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The Glorney-Raisbeck Fellowship in the Medical Sciences will be awarded by the Committee on Medical Education of The New York Academy of Medicine for one year of research and/or study in any field of medicine or its allied sciences. The initial award will be for the academic year beginning July 1, 1961. Under circumstances deemed appropriate by the Committee, the Fellowship is renewable on a year-to-year basis for two additional years.

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A candidate should be prepared to give assurance that he will have an institutional appointment which will enable him to carry out the objectives of his program of research and/or study. Such institutions will be encouraged to supplement the Fellowship stipend. Candidates also should be prepared to be interviewed by the Committee (out-of-town candidates at own expense).

Deadline for receipt of applications is *SEPTEMBER 1, 1960.*

Requests for application forms and additional information should be addressed to:

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The New York Academy of Medicine
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DATA ON INTERNATIONAL CONGRESSES REQUESTED BY LIBRARY

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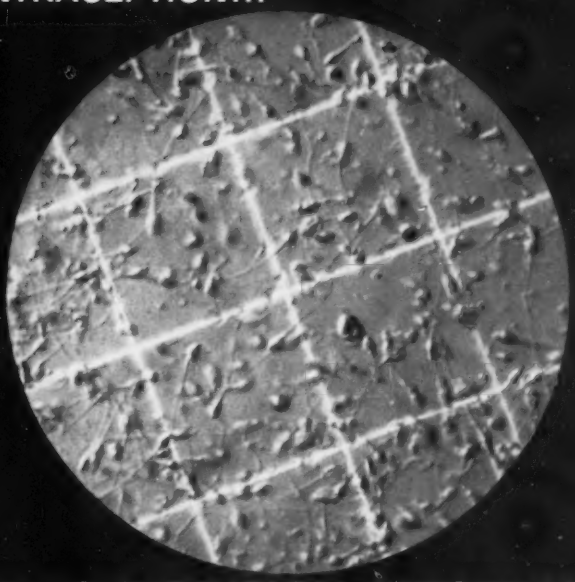

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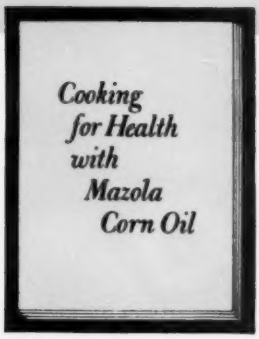

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Natural Tocopherols . .	about 0.1	0.015
Cholesterol	None	None
Salt (Sodium chloride) .	None	None

Calories—125/tablespoon

SELECTED BIBLIOGRAPHY: The methods and effectiveness of practical changes in dietary fats for hypercholesterolemic patients have been reported in numerous papers. Some recent ones are: H. B. Brown and I. H. Page. J. Am. Med. Assoc. *168*, 1989-95 (1958). N. Jolliffe, S. H. Rinzler and M. Archer. Am. J. Clin. Nutrition 7, 451-62 (1959). L. W. Kinsell, G. D. Michaels, G. Walker, P. Wheeler, S. Splitter and P. Flynn. Diabetes 8, 179-88 (1959). P. A. Stefanik and M. F. Trulson. Postgrad. Med. 26, 533-8 (1959).

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*Knudsen, E. T., and Rolinson, G. N.: Lancet 2:1105 (Dec. 19) 1959.

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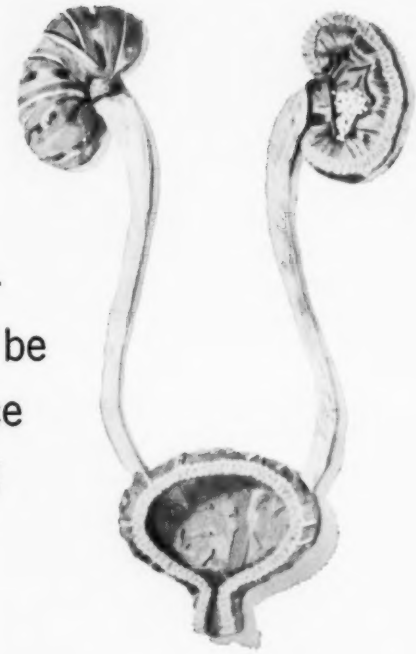
Just a "simple" case of cystitis may be the precursor of pyelonephritis[1]— or may actually be the first evidence of a pre-existing pyelonephritic process.[2]



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REFERENCES: 1 Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

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Can the proper use of alkaline waters help lower mortality rates in cardiovascular diseases?

Schroeder[1] notes that geographic variations which occur in the incidence of and death rate from atherosclerotic heart disease cannot be explained on the basis of racial backgrounds, local dietary habits, sources of food, or environmental stresses and strains. Therefore, it is possible that "some widely variable environmental influence or influences, geographically linked" may affect the incidence of this disorder. Since one factor to which all populations are exposed is drinking-water, an analysis of the relationship between the drinking-water in various cities and states and the incidence of cardiovascular and other diseases was undertaken.

Data on the water were obtained from a detailed analysis of samples of water from 1,315 cities in the United States, made by a United States Geological Survey in 1950-1951. It was found that in regions in which the water was characteristically "hard," the incidence of atherosclerotic and other degenerative types of heart disease was low, and vice versa. This correlation did not obtain in the case of noncardiovascular diseases. Factors in the water which were connected with its state of "hardness" and thus had an apparent protective effect included magnesium, calcium, sulfate, fluoride, silica, total solids, specific conduction (a measure of ionizable materials in solution), bicarbonate content, and alkaline pH. It would appear that some factor either present in hard water or missing in soft water affects the death rate from degenerative cardiovascular disease.

[1] Schroeder, H. A.: Relation Between Mortality from Cardiovascular Disease and Treated Water Supplies. Variations in States and 168 Largest Municipalities of the United States. *J. A. M. A.* 172:1902 (Apr. 23) 1960.

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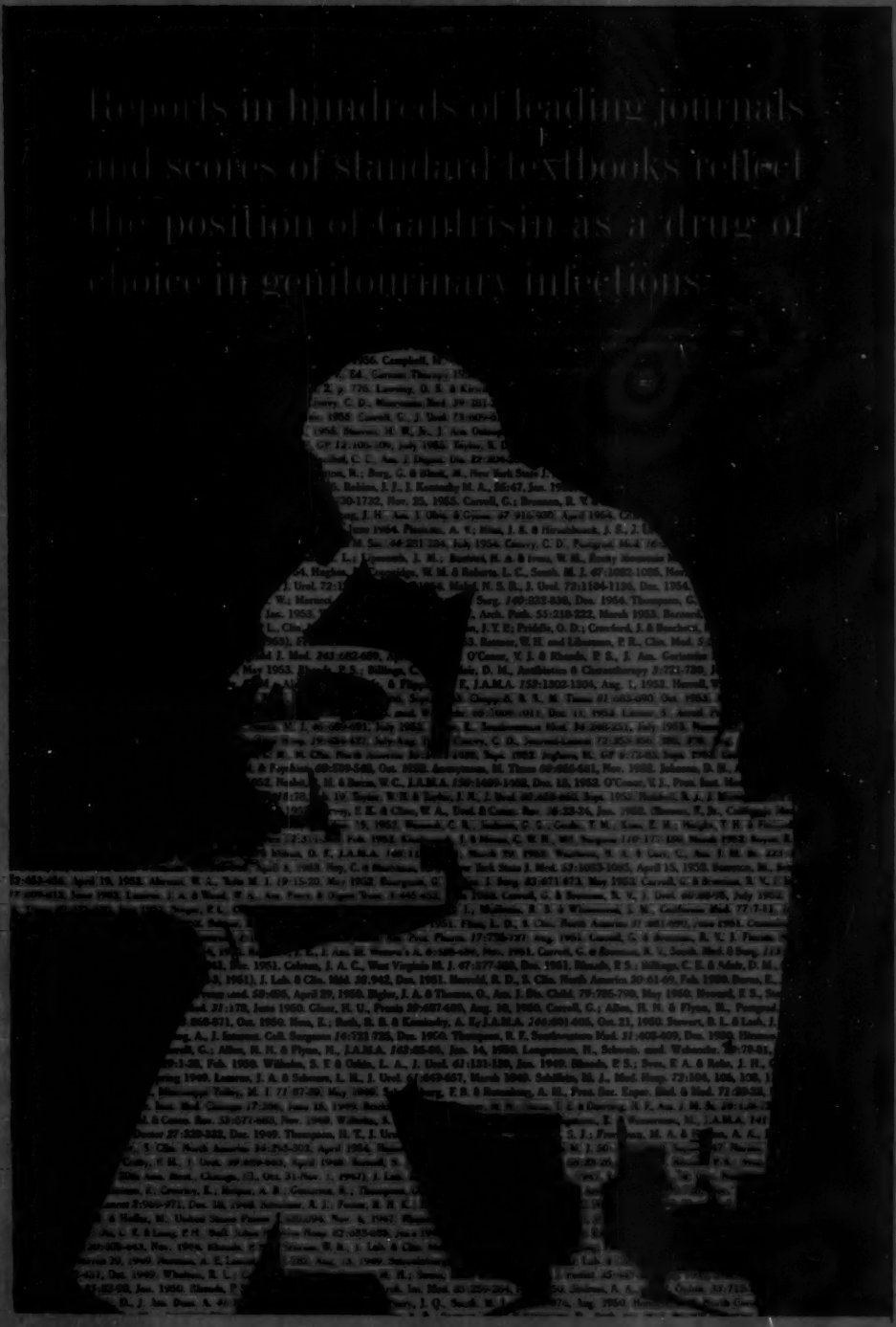
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